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NUTRITIONAL DEFICIENCY *

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NUTRITION is the process of using substances derived from food for growth and for maintaining the integrity of the living organism. It consists, as McCarrison [1] has stated, in the taking into the body proper and in the assimilation there of materials with which the tissues of the body are built up, their waste repaired and their deterioration prevented. The materials affecting the function of nutrition are oxygen, water, protein derivatives, fats, carbohydrates, mineral elements, and vitamins, among which may be included material effective in pernicious anemia. Nutritional deficiency may arise from insufficient energy production as a result of an inadequate caloric intake, but it is protein, vitamin and mineral deficiency that commands our attention today.

"Deficiency disease" is a term which by custom was applied first to conditions where the causal factor was deficiency of vitamins in food, and more recently has been used to include disorders arising from lack of minerals and other nutritional factors. Nutritional deficiency disease is apt to be still thought of as arising only from a dietary defect. Nutrition, however, depends upon not only what man decides to eat but on numerous other factors such as the digestion, absorption, and proper utilization of sufficient amounts of the 36 or more substances required for health. Vitamin and mineral deficiency disease can be profitably thought of as due to the failure of consumption or lack of utilization or loss from the body of these essential factors. The nutritional essentials, the lack of which causes deficiency disease, serve as chemical links in the chain of normal metabolism and can not be manufactured by the body from purified fats, carbohydrates and proteins. It is natural that a defect of diet should be considered the cause of vitamin deficiency. However, on reflection it is at once apparent

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that the more proximate factor is the exhaustion or loss of the vitamin by the body through natural metabolic processes. A defective diet may be the cause of the disturbance but only through failure to replace the defect within the body. Thus, defective food can not be considered the cause of deficiency disease in quite the same sense, for example, that infected food is recognized as responsible for typhoid fever or botulism.

The Effect of the Utilization of Energy

The effect of the utilization of energy on the production of vitamin deficiency is significant. In general terms the greater the chemical activity the more rapid is the depletion of substances in the bodily environment, the lack of which is responsible for nutritional deficiency disease. Thus, although in complete starvation the vitamin intake is nil, starvation is seldom associated with signs of vitamin deficiencies, in part perhaps because the metabolism is depressed and in part because there is insufficient time for the exhaustion of the vitamin stores before death ensues from general inanition. On the contrary, when the caloric content of the diet is high or the total energy expended is high and the vitamin intake is low, vitamin deficiency in many instances develops relatively easily and rapidly. The ease with which a variety of vitamin deficiencies develops in individuals who chronically imbibe large amounts of alcohol and who are very apt to select a poor diet, serves as a striking example; although very many calories may actually be derived from distilled spirits they supply none of the other nutritional essentials.

That exhaustion of the supply of nutritional factors in the body is the essential basis of deficiency disease is also indicated by the fact that such disorders are particularly apt to develop at a time in life when the demands for these factors are greatest, namely in infancy and childhood, owing to growth, and in pregnancy and the puerperium when the physiological strain of child-bearing and lactation requires dietary factors to be from 10 to over 100 per cent greater than the standard requirements for normal women.

The effect of an increased expenditure of energy on the precipitation of deficiency disease is to be observed where scurvy and beri-beri are endemic because these conditions are prone to develop in individuals undertaking the greatest amount of physical exertion. It was recognized by navigators of the seventeenth century that sailors undertaking the hardest labor were affected by scurvy before the men occupied with duties calling for little physical strain. Pathological disturbances such as thyrotoxicosis leading to accelerated oxidation processes may also affect the ease with which deficiency syndromes appear.

Distinctive data concerning the relationship between vitamin requirement and total metabolism have been given by Cowgill[2] for vitamin B_1 (thiamin). His studies indicate that deficiency of this vitamin arises more readily as the total metabolism increases if the intake of vitamin B_1

remains constant. Protection against vitamin B_1 deficiency fails if there is a low vitamin B_1-calorie ratio or, as Williams and Spies [3] have suggested, a low vitamin B_1-non-fat calorie ratio. This state of affairs is common in chronic alcoholism. In this condition other factors act to enhance vitamin B_1 deficiency in the body proper but the low vitamin-calorie or non-fat calorie ratio is important in the production of polyneuritis, disorder of the heart, and other manifestations of a deficiency of this nutritional essential.

The influence of excessive calorie intake from food itself on the production of vitamin B_1 deficiency is illustrated perhaps by the following case.

The patient was a man, usually weighing 160 pounds, who had gained about 55 pounds in a year because of eating excessively, particularly of sugar and fat. He did this because he suddenly became rich and declared he had always wanted to eat "luxuriously." Signs attributable to vitamin B (complex) deficiency developed; neuritis in particular. This patient reduced his diet by omitting sugar, chocolate, butter (except about 20 grams) and olive oil, but made no other change so that the vitamin B_1 content remained about the same. His weight fell slightly more rapidly than it was gained, reaching 165 pounds 10 months later. Within two months after commencing this reduced diet, signs of neuritis and vitamin B (complex) deficiency had vanished. When the patient found that he could reduce his weight, he decided that since he enjoyed the foods omitted he would again eat excessively. His weight soon increased and polyneuritis returned, to vanish soon after he ate in a reasonable manner and partook of a concentrate of vitamin B.

The Influence of the Gastrointestinal Tract

Defective diets are, of course, a most important cause for nutritional deficiency. Defective nutrition, however, can arise even when the diet seems adequate, because of some disturbance in the state of the gastrointestinal tract and its contents which may act adversely so as to "condition" or enhance a deficiency of nutritional factors within the body proper. The difficulty may depend on the improper reduction of raw materials to the correct size and constitution for absorption, as can arise for example from lack of teeth, diarrhea, or defective gastric secretion. Simple tests to determine defective absorption are needed. Failure of this normal function of the alimentary tract alone may prevent the body itself from receiving proper amounts of nutritional essentials. Furthermore, as McCarrison originally showed, widespread changes in the gastrointestinal tract can be produced by defective nutrition. Such alterations can impair absorption leading to a further deficiency of nutritional essentials and a vicious cycle is thus established. There are innumerable factors that have to do with absorption and the disturbances may be anatomical or chemical and physiological. Alterations in motor and secretory functions, the composition of the intestinal contents and the influence of effects arising from an origin external to the alimentary tract may affect absorption. One must distinguish between the effects being primary or contributory, for disease itself can cause all sorts of dysfunction of the intestinal tract. The statements

to follow simply indicate some of the known relationships between gastrointestinal function and nutrition.

There is little direct evidence regarding faulty absorption from the human gastrointestinal tract but, as is indicated below, there is a considerable amount of indirect evidence. Perhaps the most direct evidence has been given by Groen's [4] studies. He has shown, by means of intubation of the small intestine, that when glucose is kept in contact with a segment of the intestine in pernicious anemia the ability of a given area of the intestine to absorb it is definitely diminished. With improvement in the patient upon administration of liver extract this function apparently often returns to normal. Difficulty in the absorption of sugars can not be ascribed only to lack of the factor needed for manufacture of normal blood because Groen has shown a similar state of affairs occurred in cases of vitamin B_1 deficiency without anemia and diminished as the patients improved upon being given proper therapy. In a case of scurvy Groen found this function normal. It is possible that this defect is due to the lack of some component or metabolic derivative of the vitamin B complex certainly contained in crude liver extracts. Likewise Barker and Rhoads [5] have shown that in sprue with intestinal symptoms the levels of the fat in the blood after a meal rich in fat are low, but that after the injection of liver extract the post-absorptive levels of fat in the blood approach normal.

Various organic abnormalities of the gastrointestinal tract are associated with the production of nutritional deficiency syndromes. Sometimes this results in producing chemical and physiological alterations which may be the more immediate cause for producing a deficient state or causing faulty absorption. Intestinal anastomoses and partial intestinal stenosis have been shown to be responsible for numerous different syndromes due to deficiency of vitamins and other nutritional essentials. The opportunity of correcting the organic defect by surgery has on several occasions resulted in cessation of the difficulty the body has had in obtaining or utilizing the factors it lacked. In pernicious anemia, for example, Richardson [6] and I have observed patients with an intestinal short circuit who maintained their blood with difficulty on liver extract administered orally, but who did so relatively easily when it was given intramuscularly. These individuals were able to maintain their blood without liver extract after the intestines had been returned to essentially their normal state by operative procedures. In such instances the influence of a toxic factor arising as a result of the intestinal disturbance and acting as an inhibitory agent may be perhaps more significant than the abnormal anatomical relations handicapping absorption. In pernicious anemia usually a disturbance of a certain portion of the intestinal tract, namely the stomach, is responsible for the profound effect upon the nutrition of the individual. This is known because Castle [7] has shown that a factor in the normal diet becomes effective in the body as "liver extract" only after interaction with a substance secreted by the normal stomach. The gastric factor is lacking in most cases of Addisonian

pernicious anemia but a deficiency of the food factor or disorder of absorption may lead to a similar syndrome and such disorders may be contributory in classical cases of Addisonian pernicious anemia.

Nutritional deficiency can disturb not only chemical and physiological functions but also cause anatomical changes in the gastrointestinal tract making it still more difficult for the body to receive the material it lacks. The lack of material found in the broader fractions of liver extract effective in pernicious anemia can lead to degenerative alterations in the gastrointestinal tract, causing atrophic changes in the tongue, esophagus, gastric mucosa, and intestines which appear clinically as signs of pernicious anemia, sprue, pellagra, and in less well defined conditions. Entirely similar alterations have been produced by Miller and Rhoads [8] in swine on diets deficient in vitamin B_2 or a closely related substance. The lack of nutritional essentials other than those of the vitamin B complex or related substances, such as vitamins A and C, can also induce degenerative changes in the gastrointestinal tract. These anatomical changes are in large part reversed following the administration of suitable amounts of the deficient substance.

With protein deficiency, edema of the intestinal mucosa may occur, leading to difficulty in absorbing the needed protein. Diarrhea may result from edema, further handicapping absorption. The vicious cycle may also be enhanced by the intake of water and salt for they will favor the development of edema when plasma proteins are deficient. If moderately large amounts of water and salt are given by clysis when protein deficiency is present, as may be done post-operatively or following loss of much blood, edema may be precipitated or increased. Experimental work and cases illustrating these problems concerning protein deficiency have been presented clearly by C. M. Jones.[9] In this connection Strauss' [10] observations on the rôle of the plasma proteins in "toxemia" of pregnancy and the value in treatment of reducing the sodium intake should be noted.

Some of the physiological and chemical alterations of the gastrointestinal tract which enhance nutritional deficiency and which may be caused by nutritional deficiency may be referred to the motor and secretory functions and to the composition of the intestinal contents. Whatever causes rapid gastric or small intestinal evacuation and alteration in the tone of these organs may diminish the amount of some nutritional factor taken into the body proper. It has been shown [11, 12, 13] by roentgen-ray studies, that in sprue changes in tone and activity of the intestine vary with the severity of the disease, and that when liver extract is given these changes decrease and become absent as the patient improves and signs of faulty absorption decrease. These alterations are not specific and consist of distortion of the mucosal pattern and a variation in the caliber of the intestinal loops. Somewhat similar alterations and lack of haustral formation have been recorded in other conditions where dietary deficiency was considered to exist, and improvement has followed administration of vitamin B_1 and other nutritional essentials.

Inadequate secretions can prevent the body from receiving from the diet suitable amounts of some nutritional factors. The lack of bile may perhaps hinder the absorption of vitamin A and material such as vitamin K, which may be of value in forming prothrombin. The results on nutrition of a lack of Castle's gastric intrinsic factor have been mentioned. The rôle that achlorhydria plays in favoring the development or increase of nutritional deficiency is not well understood, but it undoubtedly is a factor of importance and has been suggested as playing a rôle in causing deficiency of various vitamins and some minerals, such as iron and calcium. This condition may be induced by faulty diets, for example, those rich in farinaceous food and sparing in animal protein. It has been suggested [14] that lack of some factor in the vitamin B complex can induce this condition. It is common, however, in various types of vitamin and other deficient states. Hypoacidity may play a part directly or indicate a significant disturbance of absorptive capacity of the alimentary tract. Lack of hydrochloric acid may decrease the ease with which substances, for example iron, are liberated from complexes which contain them in food and alter the reaction of the intestinal contents in such a way as to handicap the absorption or utilization of substances.

The mixture inside the gastrointestinal tract can influence what the body receives. For example, large amounts of some substances such as fatty acids and phosphorus may bind other substances such as calcium and iron into insoluble forms. During digestion the combined effects of low oxygen tension, an abundance of readily oxidizable substances and an acid reaction provide conditions in which the conversion of ferric to ferrous iron (the form in which iron is absorbed) is likely to occur. The mixture of the intestinal contents may be such as to injure a nutritional factor such as vitamin C, as has been suggested by various reports.[15, 16, 17] Like other conditions it may not be possible to alleviate scurvy by the oral administration of the needed substance but only by its injection and, in scurvy, although a disorder of absorption may occur, in rare cases a destruction of the vitamin may perhaps take place in the intestinal tract. It is possible that occasionally the intestine may contain particular substances that inhibit absorption. There are suggestions in the literature that iodoacetic acid can inhibit this function.

Effects produced on intestinal tract function from an influence arising external to this system must also be considered. Liver disease can increase the tension in the portal system and this may affect the absorption of material derived from food. Infections may cause low absorption. Heymann's [18] studies disclosed that 70 per cent of ingested carotene was absorbed by normal infants whereas only 36 per cent was absorbed in infants with infections. Sometimes the amount of a given substance in the body may perhaps determine the amount absorbed. McCance and Widdowson [19] have suggested that iron metabolism is regulated by controlled absorption. They consider that the amount absorbed depends perhaps not upon the con-

centration of free ions in the lumen of the gut but upon their relative concentration in relation to the level of the plasma iron and the amount of iron in epithelial cells. The absorption of calcium can be related to vitamin D, it being impaired with vitamin D deficiency. Verzar [20] has presented interesting studies concerning the rôle of secretion from the adrenal cortex on intestinal absorption and suggests that celiac disease (Gee-Herter's disease) and "non-tropical" sprue may be possibly "adrenocortical or interrenal disturbances of absorption." Studies have shown that in adrenalectomized animals a series of syntheses important for absorption and other metabolic activities are lacking, including the syntheses of fat and the transformation of lactoflavin in the intestinal mucosa to flavin phosphoric acid (one of the entities of vitamin B_2).

It is possible that some hormone of the pituitary may in part control tone and motility of the gastrointestinal tract, and the cases of pituitary disease and macrocytic anemia reported by Snapper et al.[21] have suggested to these authors that the secretion of Castle's gastric factor might be affected by some pituitary secretion. Of course, many external influences can affect digestion such as exercise, emotional reactions, and the like, and such conditions always have to be reckoned with in considering function of the intestinal tract in relation to nutrition, and are particularly important to consider in the treatment of the patient himself.

The Influence of Defective Intermediary Metabolism and Inhibitory Factors

Even if the body proper has received the usual requirement of nutritional essentials, a deficiency may arise, or more often be enhanced, because of a disorder of their metabolism. The fact that some cases of pernicious anemia require much larger doses of liver extract parenterally than other cases to maintain their blood suggests differences in the intermediary metabolism of "liver extract." Cases showing intrinsic resistance to vitamin D [22] and to other substances also occur when there is no entirely satisfactory explanation for the difficulty. It is well recognized that infection and severe damage to important organs can precipitate deficiency syndromes and that under such circumstances more of the materials lacking in the body must be given for cure. This applies to material given orally or parenterally so that faulty absorption is not the only way such disorders may act to handicap the action of nutritional materials. The increased metabolism resulting from fever does not seem to wholly explain the inhibitory or precipitating effect of infection. Many studies in recent years regarding the metabolism of vitamin C are among those that illustrate very well that infection decreases the amount of a nutritional essential available in the body for utilization. Here again a vicious cycle may arise for resistance to infection is lowered by poor nutrition and infection intensifies nutritional deficiency. There is some evidence that chronic fatigue also acts to hinder the utilization of nutritional material.

It is not surprising in view of the rôle played by infection in deficiency syndromes that Eijkman originally thought that vitamin B_1 deficiency was due to intoxication. The fact that large amounts of carbohydrate can impair the protective power of vitamin B_1 in relation to the nerves certainly might suggest that a toxic action was responsible for the condition. The pyruvate and lactate that accumulate from deficiency of vitamin B_1 can act as toxic substances, but they are not primarily responsible for symptoms of vitamin B_1 deficiency.[23] Failure of function of the cell from interference with its metabolism due directly to B_1 deficiency is the fundamental cause of symptoms. The rôle that two or more factors may play in causing disease is significant and toxic substances can precipitate symptoms of deficiency. Rhoads' [24] studies showing that indol in an amount that causes no anemia in dogs fed a normal diet can produce anemia when dogs are fed a diet which causes black tongue are most significant. The condition can be prevented and cured by liver extract. Miller and Rhoads [25] have also shown that the susceptibility of the canine hematopoietic function to damage by amidopyrine is influenced by diet. Substances may act perhaps to deplete reserve supplies, as has been shown experimentally by White [26] to be the action of iodoacetic acid on the sulphur containing amino acid reserves.

Disease of the liver can adversely affect nutrition. It can prevent the adequate storage of vitamin A and adversely affect the metabolism of carotene. The liver influences in some unknown way the metabolism of vitamin D. With severe damage to the liver it is necessary to give much larger doses of this vitamin than usual to cure rickets.[27] Plasma protein depletion is enhanced by liver disease. Nutritional factors can also alter liver function. The amount of fat stored in the liver can be related to the vitamin B_1 intake.[28] The effect of a superabundance of nutritional essentials in favorably influencing liver disease is worthy of much more study. Patek [29] and Goodhart and Jolliffe [30] among others have indicated the advantages of such treatment.

Inside the body the balance between one substance and another may influence the availability of a nutritional factor as has been noted concerning vitamin B_1 and an excess of carbohydrate. Another example is that lactoflavin has a sparing effect on vitamin B_1.[31] If one keeps in mind the rôle that such substances as vitamin B_1 play in intermediary carbohydrate metabolism and vitamin C in the balanced chemistry of oxidation reduction, it is not difficult to visualize the many ways that may bring about the improper utilization of nutritional essentials inside the body.

Depletion of Nutritional Essentials by Loss from the Body

It has been noted that nutritional deficiency disease arises because of a failure of consumption or utilization of essential factors. Increased chemical activity may enhance their depletion. Depletion may arise because of a defective diet, abnormality of gastrointestinal function, and disorder of inter-

mediary metabolism. Damage to organs and their altered function, infections, and toxic substances may act in an inhibitory way to intensify a deficiency. There is another method by which depletion of nutritional factors may arise, namely, loss from the body of the formed essentials. In pregnancy some nutritional elements must be given to the fetus, thus diminishing the mother's supply. Protein may be lost through the kidneys, into effusions in the peritoneal and pleural cavities and from suppuration and serous drainage from surgical wounds.. With loss of blood essential elements leave the body. Iron deficiency is more often attributable to chronic loss of blood than to any other mechanism. More than one of the different mechanisms that induce nutritional deficiency are usually active in any one case. The physician should recall this in practice and attempt to correct all possible faults that might handicap nutrition.

Remarks Concerning Diagnosis, Treatment, and Particularly Prevention

An appreciation of the nature of nutrition and of the mechanisms involved in producing nutritional deficiency forms the background upon which diagnosis, treatment, and prevention depend. There follow a few remarks concerning these aspects with especial emphasis on that most important problem, namely prevention.

Nutritional failure in practice is seldom complete or simple. It is often complicated by a variety of mechanisms inducing its origin or aggravating the initial abnormality. The occurrence of a mild state of suboptimal nutrition or a borderline state of partial deficiency is very common and examples of classic scurvy, beriberi and the like are relatively rare. Whenever there is evidence that one nutritional essential is lacking, leading to a clear cut syndrome, it is usually possible to show that deficiency of other factors exists so that multiple deficiency is the rule. Signs indicative of outstanding deficiencies of two or more factors in one individual are not rare. An era appears to be approaching when by quantitative chemical tests, some of which are well developed and others under study, it may be possible to appraise the nutritional status of an individual. For some time yet we must be satisfied to diagnose in many instances of partial deficiency that such a condition merely exists without being able to name with any precision exactly what factors are lacking. Even when outstanding signs of deficiency are present it is often impossible to state exactly what missing factor is responsible for each and every manifestation although, of course, there are certain signs characteristic of deficiency of each vitamin and mineral, and the like. Multiple manifestations can be related to a single deficiency. We must, however, attempt to define and learn in exactly what way symptoms and signs found in deficiency states are produced.

The prevention of nutritional instability is of prime importance. Often the results of pronounced deficiency are not reversible as, for example, the

bone deformities resulting from rickets, the loss of the teeth from scurvy and central nervous system degeneration in pernicious anemia. On the contrary certain defects can be repaired, such as the damaged capillaries in scurvy and the blood in pernicious anemia. It is the vague borderline states of nutritional failure of mild degree that are of great importance to recognize and correct, and here we usually have to be guided by general symptoms, a detailed history, and hints obtained from various sources including newer chemical and other tests.

The early general symptoms of nutritional deficiency are vague; a sense of fatigue or lack of energy, inefficiency, and mental irrritability are common. Mild anemia and simple disorders of the digestive tract are the rule. Symptoms and signs of deficiency may be referable to essentially any tissue of the body but disorders referable to the bones, faulty growth, the gastrointestinal, neural, blood-forming and reproductive systems, and the skin are particularly common. The history may indicate that the patient is nervous, has a poor appetite, mild digestive symptoms, and is fussy and finicky regarding his choice of food. He may be in such haste that he has not time for a proper luncheon and is too tired to eat a proper meal in the evening. As a result the individual is easily exhausted and nervously unstable. The exact deficiency present can not be stated but proper food will go a long way to improve such a patient.

There is a wide range between the minimal and optimal requirement of dietary factors and studies concerning this subject are few. Those made on the utilization and retention of vitamin B_1 in children by Knott [32] are significant in this respect. She has shown that a definite trend toward higher retention of vitamin B_1 accompanies higher levels of intake. The level of vitamin producing the highest retention may be considered optimal and the wide range observed between minimal and optimal requirement aids to explain the existence of mild vitamin B_1 deficiency in children and the beneficial results obtained by the addition of vitamin B_1 to the diet.

We should be alert to detect physiologic changes due to deficiency long before gross pathologic alterations appear. Such conditions as a low content of vitamin C in the blood and urine and slight subnormal ability to adapt vision to darkness (associated with insufficient amounts of vitamin A) often occur in individuals who consider themselves well and who show no other signs or symptoms associated with deficiency. These changes can be corrected by supplying the deficient substance. Although no one positively knows what harm slight physiologic alterations of nutritional factors cause in apparently otherwise normal persons, they certainly can not be looked upon as desirable conditions for health. The subtle effects produced by long standing slight nutritional defects need evaluation, but in practice they should be prevented if possible. In considering the far-reaching influences of faulty nutrition it should be recalled that there is evidence that it may affect adversely the span of life and that the undesirable effect of a faulty diet in the zone of partial deficiency may become detectable

only after years or generations, and that a deficient diet may impair the vigor and resistance of an individual for some period after he partakes of an adequate diet. In this connection the observations of Bloomfield and French [33] on rats are of interest. They observed that comparable rats on the same defective diet showed great individual variation in weight loss. A long time after the weight loss had been restored by a normal diet the rats were subjected to the same deficient diet and the same animals which lost the most weight were the ones to do so again and even more rapidly a second time.

The activities of the League of Nations and the national alertness to the importance of proper nutrition in the development of the child, in the prevention of disease and for buoyant rather than merely satisfactory health is of great significance to mankind. Educational efforts can lead to improvement of the nutritional status of a large number of individuals, and in so doing, as McLester [34] has noted, the essential nature of any one food factor or group of factors must not be emphasized. Faddism is a cause of nutritional failure. The doctor must keep in mind that an optimal diet leads to better health than many usual diets with minimal requirements of some essential substances. He must not only be able to advise groups of individuals, such as pupils in school, regarding diet, but be alert to prevent nutritional disorders in a given patient. His attention, for example, to the iron, protein, and sodium intake in pregnancy will minimize anemia and toxemia. It is well to remember that since the nutritional states of mothers affect the well being of infants, the health of the whole population depends to a greater or less extent on maternal nutrition. Likewise, let us recall that at no period of life is optimal nutrition more important than in infancy and childhood, because nutritional defects so readily produced then may be at the root of disorders arising at any time later in life. The physician will observe many patients of all ages with mild symptoms where meticulous attention to diet will improve their well being. He should be conscious that a nutritional defect may exist and play a rôle of importance in many patients whom he sees when the symptoms presenting would not readily suggest that a better diet would be of distinctive value. The frequency of abortion has been shown to be diminished in individuals placed on optimal diets, and decrease of nervousness and better attention to school studies may occur when the pupil partakes of a diet unusually rich in protective foods. Faulty nutrition may act to spring a trap which aids to produce a condition which diet does not correct. Hertz and Means' [35] observation that pronounced weight loss may be a precipitating factor in thyrotoxicosis is of this sort. It is possible, I believe, that such a disturbance may play a rôle in an occasional case of leukemia.

If a deficiency syndrome is clear cut, specific treatment must be employed. The oral route often suffices. Today, however, the availability of preparations of vitamins for injection permits large amounts to be placed easily in the body proper and is of great value in the treatment of

severe cases and sick individuals. Satisfactory results will often be obtained only when distinctly large amounts are given. The rapid and dramatic improvement seen upon injection of vitamin B_1 in cases of heart disorder and polyneuritis associated with its deficiency and the striking effects of nicotinic acid in pellagra are among other examples of the value of modern therapy in deficiency disease. When specific therapy is given an attitude must not be taken that it is not necessary to watch the patient closely and that no more need be done than administer the substance in question. In the early days of specific treatment adverse symptoms occasionally appear arising from the material given, for example, tetany in rickets requiring the intravenous administration of calcium, and edema in pernicious anemia, about the time the patient begins to sit up, which clears as liver extract is continued. The deficient state must be met in toto and, as the patient improves following specific therapy, attention must be given to all aspects of his case.

In spite of the fact that diagnosis of the exact deficient state must be made as accurately as possible, it is often of more practical importance to recognize that the patient has nutritional deficiency than to be able to name exactly what nutritional deficiencies he has. In many cases of mild deficiency the precise condition can not be defined and in an effort to correct the condition the administration of supplements of manufactured concentrates alone will not at present solve the problem. As has frequently been stated experience tells us that a mixed diet of natural food stuffs, one especially rich in milk, green vegetables, fruit, butter, eggs and food with ample protein of good biologic value gives the best results.

Concluding Remarks

Ideally we should have no cases of nutritional deficiency to treat for if we lived in a Utopian world preventive measures would banish their existence. This would not be brought about by diet alone because, as has been discussed, there are many other factors than diet that play an important rôle in establishing nutritional deficiency in man. If, however, the optimal, *not the usual,* diet for man at all ages and under varying circumstances of his activity and environment were known, and if throughout generations each person took an ideal diet—one nicely adjusted to all its constituents at an optimal level for the best possible achievement—not only would much illness be prevented but the physical and mental development of man would be improved.

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STUDIES ON THE PATHOLOGICAL PHYSIOLOGY OF THE EXOPHTHALMOS OF GRAVES' DISEASE *

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THE chronic progressive exophthalmos of the type seen in Graves' disease, even when uncomplicated, is obviously a highly complex phenomenon, perhaps as complex etiologically as Graves' disease. Although both have been studied for more than a century they are still involved in doubt and controversy.

My primary interest in the study of exophthalmos has been the hope that a further understanding of this symptom might throw additional light on the etiology of Graves' disease. There is also the immediately practical question of how to continue subtotal thyroidectomy in the treatment of Graves' disease and at the same time prevent the occasional development of so-called "paradoxical" or "malignant" exophthalmos.

The exophthalmos of Graves' disease is a chronic, progressive, bilateral protrusion of the orbital contents. One says 'bilateral,' though rarely it is unilateral, and usually it is not symmetrical, either in man or in animals —of the animals so far studied it is most asymmetrical in the guinea pig. This form of exophthalmos is also seen occasionally in human rickets [1] and may be produced experimentally in the severe low P rickets in rats (Thompson [2]). It is also seen in acromegaly,[3] in the leukemias,[4] in chronic nephritis,[5] and in experimental chronic renal insufficiency. Possibly, the forms seen in congenital syphilis [6] and in the Hand-Schüller-Christian syndrome [7] may be of this type. Exophthalmos is usually a late symptom in all of these diseases, just as in Graves' disease. It is present in about two-thirds of the cases of primary Graves' disease, i.e., below the age of 45, but it is relatively infrequent in those cases developing during the decline of sexual life (toxic adenoma, adenomatous goiter, iodine Basedow, menopausal Graves'), so that if all cases, irrespective of age and sex are included, it is present in about one-third of the cases.

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Basedow [8] thought it was due to a hypertrophy of the cellular tissues in the orbit. Sattler,[9] W. Krauss [10] and many others thought it was due to venous congestion and edema. After the demonstration by Askanazy [11] of fatty degeneration of the recti muscles in Graves' disease and the occurrence of a chronic inflammatory swelling of these muscles in the late stages of severe exophthalmos (Naffziger [12]), the view that the exophthalmos was due to enlargement and weakness of these muscles was advanced. Supplementing all these theories is the idea that an increased normal or

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abnormal thyroid secretion is also necessary. None of these theories is now considered of primary importance, since the exophthalmos, at least in its earlier stages, shows considerable variation from day to day, both in man and animals, and also may disappear after death, or under general anesthesia, or after section of the cervical sympathetic. However, the degenerative and inflammatory changes mentioned above are unquestionably important secondary, complicating, and even contributing factors, but in my opinion are always the result and never the cause of exophthalmos.

The experimental study of exophthalmos began in 1858 with the discovery of H. Müller [13] of the smooth muscles of the orbit of mammals. Müller recognized two groups of these muscles: (1) *periorbital,* and (2) *palpebral muscles.* The *periorbital muscle* is well developed in lower mammals and consists of a muscular cone whose base is attached to the orbital septum and bony rim of the orbit and whose apex is attached to the ring of Zinn. In amphibians, reptiles, birds and some aquatic mammals (seal, dolphin) the muscle fibers have cross striations. This is a powerful muscle and envelops the entire contents of the orbit except the lacrimal gland. In the lower mammals it is capable of pushing the orbital contents forward when electrically stimulated in spite of the normal antagonism of the recti and retractor bulbi muscles. This was first demonstrated by Wagner in 1859 [14] and more extensively studied by Claude Bernard, Aran and others. MacCallum and Cornell [15] (1904) by removing the roof of the orbit in the dog and stimulating the cervical sympathetic, observed typical smooth muscle contraction waves passing back over the muscle.

In man and the anthropoids, the periorbital muscle is vestigial and because of this most students have rejected the idea that its contraction can have any influence on the position of the orbital contents in man. We know that cutting the cervical sympathetic causes a Horner's syndrome in man just as in animals, although the ensuing enophthalmos is not quite so striking in man. The *palpebral muscles* of Müller are present in both the upper and lower lids only in man and anthropoids. In the lower mammals palpebral muscles composed of smooth muscle fibers occur only in the lower lid and in some mammals (seal and dolphin) these muscles also are striated. These involuntary palpebral muscles in man form an incomplete ring around the globe (Hesser [16]) and ancestrally are derived from the striated recti muscles. In 1907 Landstrom [17] described a cylinder of smooth muscle fibers inserted into the fascia of the globe near its equator and extending anteriorly to the orbital septum. Evidence for separating such a group of muscle fibers from the palpebral muscles of Müller seems inadequate. No one doubts that lid-lag (von Graefe's sign) and widening of the palpebral fissure (Stellwag's and Dalrymple's signs) are principally due to increased tone of the palpebral muscles of Müller. It is only the protrusion of the globe in man by the increased tone of the vestigial periorbital muscle that is doubted, even though section of the cervical sympathetic may instantly abolish the exophthalmos and lid spasm and produce

enophthalmos in man as well as in animals. As above mentioned, this muscle is fully capable of protruding the orbital contents in the lower mammals, but in man and in monkeys it seems to be inadequate and one has to invoke the additional factor of a weakness of the recti or antagonistic muscles to account for the exophthalmos of Graves' disease.

The sympathetic innervation of the muscles of Müller as shown by Claude Bernard may be represented schematically by ganglion cells in the lateral horns of the spinal cord, whose axones emerge at the level of the first and second dorsal vertebrae, and end around the ganglion cells of the superior cervical ganglion from which the postganglionic fibers extend to the muscles. In 1909 Karplus and Kreidl [18] showed that stimulation of the hypothalamus in cats, laterally and slightly posterior to the infundibulum, caused maximum dilatation of the pupil, widening of the palpebral fissure, and thus established true sympathetic representation in the hypothalamus. The pathway from the hypothalamus to the lateral horns of the spinal cord is unknown.

In 1910 Gley [18a] reported the development of exophthalmos in one male puberal rabbit following thyroidectomy. In 1931 Schockaert,[19] working with baby ducks, and Loeb and his co-workers,[20] using young guinea pigs (adults are highly resistant), observed that exophthalmos developed in from seven to ten days following the daily injection of anterior pituitary extracts. In 1932 Marine, Baumann, Spence and Cipra [21] reported the occurrence of exophthalmos in puberal rabbits that developed parenchymatous goiter on a diet of alfalfa hay and oats and the daily intramuscular injection of 0.1 c.c. or more of methyl cyanide. The fact that exophthalmos did not develop until large parenchymatous goiters appeared and that such goiters were associated with hypertrophy of the anterior pituitary of the type seen after thyroidectomy suggested that there was a close association between thyroid deficiency and increased activity of the anterior pituitary and exophthalmos. Accordingly, we removed the thyroid from rabbits and found that exophthalmos was more easily and more quickly produced.[22] By analogy it also seemed likely that the production of exophthalmos in guinea pigs by anterior pituitary extracts would be facilitated by thyroidectomy. This also was found to be true and indicates that the exophthalmos promoting effect of anterior pituitary extracts is brought about by action on other end organs than the thyroid.[23] Smelser has reported similar observations.[24] The observations of Friedgood [25] on guinea pigs further confirmed the importance of thyroid deficiency. He found that the best exophthalmos produced by anterior pituitary extracts developed after the metabolic rates had fallen below normal. It was now established that the thyroid hormone took no positive part in the production of exophthalmos and also that some substance produced in the anterior pituitary was directly, or indirectly through its interrelations, responsible for the exophthalmos, possibly by acting on a sympathetic nervous mechanism within the central nervous

system (hypothalamus). Pituitary extracts will not produce exophthalmos if the cervical sympathetic is cut.

It is well known that exophthalmos cannot be produced by the administration of thyroxine or desiccated thyroid either in man or in animals, despite occasional positive reports in the literature (Notthafft,[26] Brain [27]). Indeed, the opposite is true. Thyroxine offers specific protection against the development of exophthalmos in rabbits, guinea pigs and probably man. It has also been shown that this form of exophthalmos may be cured in

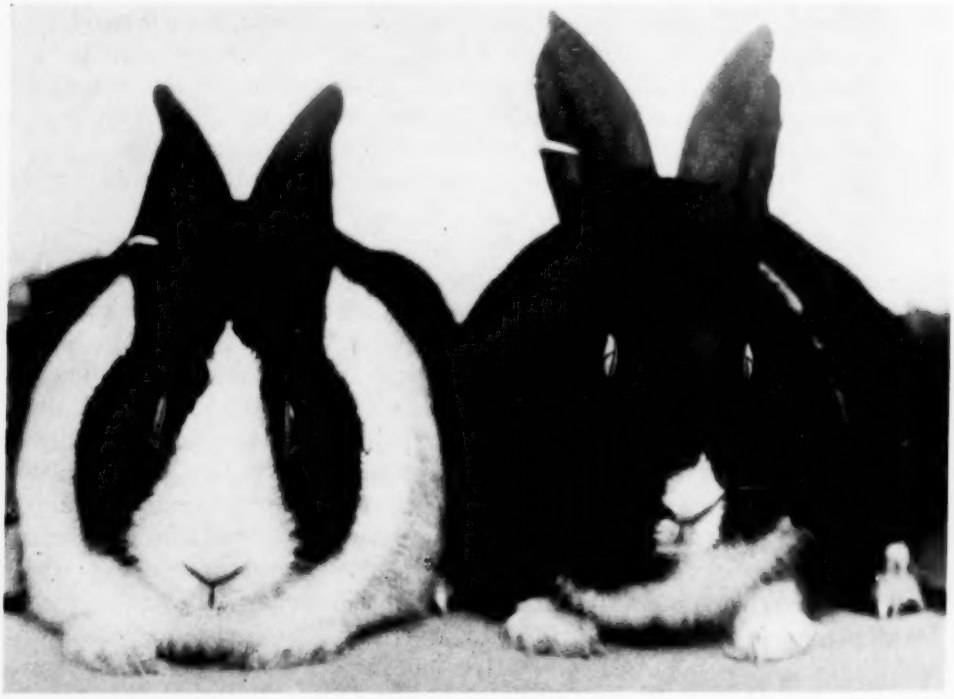

FIG. 1. March 6, 1935. Moderate exophthalmos post-thyroidectomy. Males.

rabbits by thyroxine (figure 2), and there is considerable evidence that thyroxine is beneficial in human exophthalmos. In the presence of abundant thyroid tissue, iodine is as effective as desiccated thyroid in preventing exophthalmos in rabbits and guinea pigs, and there is rapidly accumulating evidence that the present wide-spread use of iodine in the treatment of Graves' disease is gradually reducing the incidence of exophthalmos in Graves' disease. Plummer and Wilder [28] report a drop from 69 to 40 per cent in the incidence of exophthalmos since 1922. The mechanism of exophthalmos production appears to be due to the action of an excess of some anterior pituitary hormone directly, or indirectly through the gonads, on a sympathetic center in the hypothalamus. Such stimulation of the sympathetic center apparently becomes effective only when thyroxine is greatly

decreased, which suggests that such centers are held in a delicate balance by the interaction of many hormonal factors. Thyroid insufficiency, relative or absolute, therefore, is a necessary condition in order that this form of exophthalmos may develop, yet it does not occur in the severe thyroid deficiencies of endemic cretinism or in Gull's disease. It is obvious, therefore, that other factors than thyroid deficiency and hyperactivity of the anterior pituitary are involved. We have many times pointed out that sex and age are important. In rabbits it is produced most easily at the age of puberty and is approximately 20 per cent more frequent in males. We have also

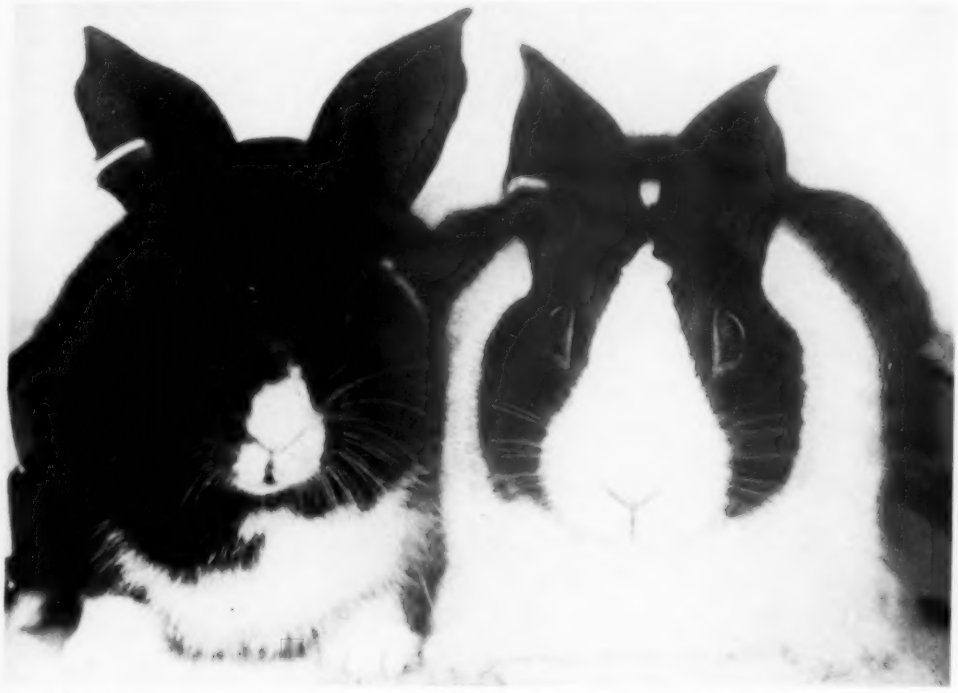

FIG. 2. April 23, 1935. Same rabbits as in figure 1, 48 days later, after having received 0.2 gm. desiccated thyroid daily during this period.

pointed out that those rabbits which develop the best exophthalmos are sexually more active. In view of the age and sex differences and of the increased sexual development following thyroidectomy in puberal rabbits, we have studied the effect of gonadectomy on the development of the exophthalmos, and found that no frank exophthalmos developed in 38 adult male and 23 adult female rabbits after gonadectomy.[29] We have also studied the effect of gonadectomy on the regression of exophthalmos in nine male rabbits and found that it regressed completely within three to five weeks, whereas it was unchanged in the controls. One of the rabbits in which regression occurred following gonadectomy had had exophthalmos

continuously for 45 months despite bilateral cryptorchidism and later unilateral orchidectomy. Attempts to analyze the sex gland factor have been made by means of cryptorchidism, by which we attempted to split the possible effect of the germinal epithelium from that of the interstitial cells. We found that exophthalmos did not recede in cryptorchid rabbits even after six months.[30] The evidence so far obtained indicates that the germinal epithelium has little, if anything, to do with the development of exophthalmos, but that the degree of functional activity of the interstitial cells is an important factor in determining the development of exophthalmos. It further suggests that the absence of exophthalmos in myxedema and in cretinism may be in some way related to the lack of development of sufficient internal secretion of the gonads as in cretinism or to the loss of some of these internal secretions as in myxedema. Following up the evidence that the interstitial cells of the testis were producing some hormone which in association with reduced thyroid secretion, increased pituitary activity and perhaps other endocrine and mineral imbalances was capable of maintaining an existing exophthalmos, we have carried out experiments on rabbits using testosterone propionate, androsterone and dehydro-androsterone. Only in rabbits that had had exophthalmos and recovered or had latent exophthalmos or had mild exophthalmos did the administration of these androgens increase or produce exophthalmos. The reactions were greatest with testosterone propionate and least with dehydro-androsterone. Feeding desiccated thyroid counteracts the exophthalmos promoting effect of the androgens.* In no instance was exophthalmos produced in rabbits that had never had exophthalmos, irrespective of whether they had been subjected to thyroidectomy, thyroid feeding, cryptorchidism or gonadectomy, suggesting that other factors must be favorable in order to obtain exophthalmos with androgens. These observations suggest that the promoting effect of androgens on exophthalmos may be an important factor in the percentile increase in the incidence of post-thyroidectomy exophthalmos in Graves' disease in males.

Why female rabbits are more resistant to the development of exophthalmos is not known, although it is tempting to suggest that the protection which oestrone gives to the anterior pituitary and its antagonistic action to androgens may be factors. The fact that exophthalmos often becomes more pronounced during menstruation, at which time the blood oestrogens are at their lowest level and the androgens relatively high, may be significant. Also in this connection the increased incidence of Graves' disease during and after the menopause is suggestive. The administration of oestrone, 100 R.U., twice daily for two months to male rabbits with fully developed exophthalmos, however, has not noticeably influenced it. There are, on the other hand, several reports of human exophthalmos having been benefited by oestrongenic substance (Halpern, 1933 [31]).

* This finding can be correlated with the well known depressing effect of thyroxine or desiccated thyroid on the gonads (depresses ovulation and spermatogenesis in rats and produces hen feathering in male birds).

Other factors are also involved. For example, the diets necessary to produce experimental goiter and exophthalmos are abnormal, particularly as regards calcium and phosphorus ratios. Reference has already been made to the occurrence of exophthalmos in high Ca low P rickets, and since the work of Aub and coworkers [32] we know that great calcium and phosphorus losses occur in typical Graves' disease, even to the occurrence of osteoporosis. Pugsley and Anderson [33] have confirmed Aub's human observations in the experimental Graves' disease-like syndrome of rats and guinea pigs produced by anterior pituitary extract. Since variations in the Ca and P ratios (particularly high P and low Ca) greatly increase the irritability of nerve and muscle cells (tetany) it is possible that the abnormal

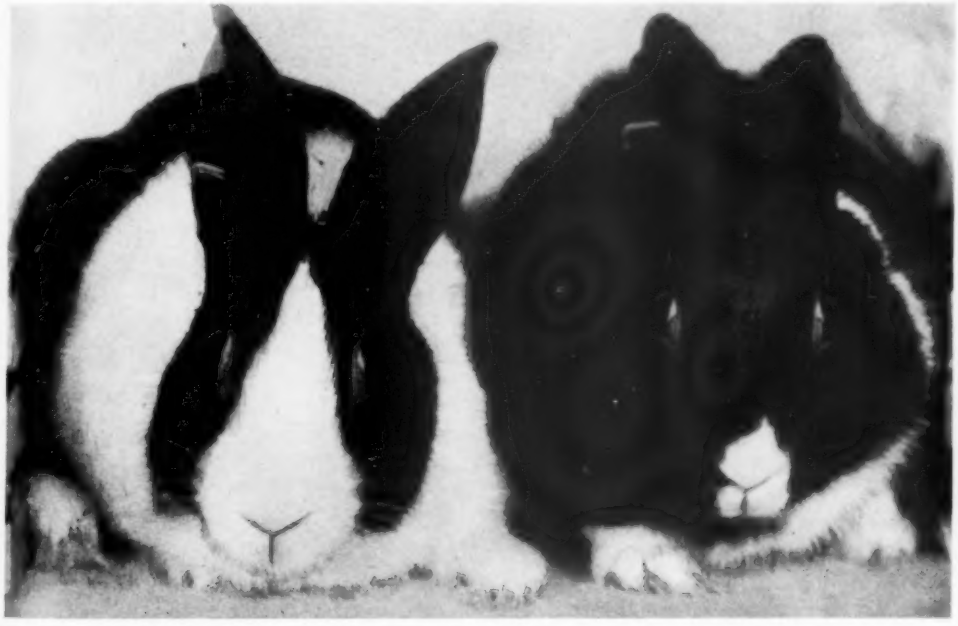

FIG. 3. July 16, 1935. Same rabbits as figures 1 and 2. Recurrence of exophthalmos after stopping desiccated thyroid.

Ca and P metabolism may be a basic factor, although nothing definite is known at present.

Finally there are some practical features that should be mentioned. It has been known since partial thyroidectomy was first introduced into the therapy of Graves' disease that occasionally exophthalmos developed or increased after the thyroidectomy. The more recent subtotal thyroidectomies associated with subnormal metabolic rates have undoubtedly further increased the incidence of post-thyroidectomy (so-called malignant or paradoxical) exophthalmos. I have collected 56 reports of such cases from the literature of the last 10 years, and in the light of the sex difference and the experimental effects of androgens, castration and cryptorchidism on exoph-

thalmos of rabbits it is significant that 60 per cent of these human cases were also in males. As regards treatment, the only medical measures that have been found beneficial are iodine and desiccated thyroid in large doses. In the light of our experiments oestrogenic substance might be combined with iodine in the attempt to further depress anterior pituitary and gonadal function in these cases. In the experimental exophthalmos of rabbits iodine in the presence of sufficient thyroid tissue or desiccated thyroid in large doses

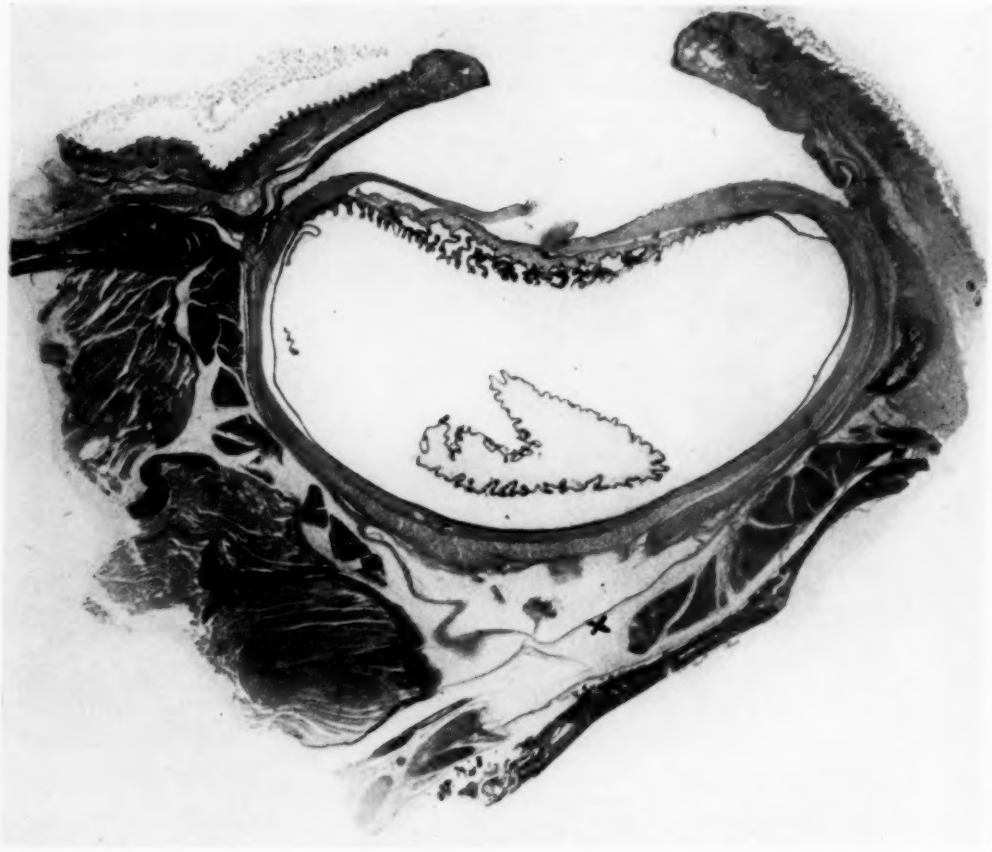

FIG. 4. Sagittal section rabbit's orbit sufficiently external to the mid-line to show the *musculus orbitalis* (marked X) as a continuous band from superior to inferior orbital ridges.

usually effects a cure (figures 1, 2, 3). In the human cases little success has been reported from the use of desiccated thyroid but most of these cases doubtless were complicated by secondary degenerative and inflammatory changes in the orbital tissues. On the other hand it may be readily prevented in rabbits and guinea pigs by iodine and desiccated thyroid. No thyroid insufficiency, no exophthalmos. All the recent literature reports indicate that it is being prevented in Graves' disease by the more extensive use of iodine that has taken place during the past 15 years. The mode of action of iodine

and thyroxine in preventing exophthalmos, I believe, is due to the maintenance of normal oxidation processes which in turn protect the pituitary and gonads from hyperactivity and in some unknown way this balance of pituitary-gonad-thyroid interrelations protects essential sympathetic nerve centers in the hypothalamus.

Regarding surgical treatment, division of the cervical sympathetic or removal of the superior cervical ganglion has been performed by Jaboulay,[34] Jonnesco [35] and C. H. Mayo [36] in man. In the experimental exophthalmos of rabbits and guinea pigs this operation completely and immediately abolishes the exophthalmos but in human cases it would not be justified in the mild uncomplicated cases where it would be effective, and it would be ineffective in those complicated by extensive organic changes in the orbital tissues. In this group the drastic operations of Naffziger and others may be indicated when life saving measures are necessary.

Summary

Thyroid insufficiency (relative or absolute) and anterior pituitary hyperactivity appear to be two of the essential factors underlying the development of the exophthalmos of Graves' disease. Yet the fact that exophthalmos does not occur in myxedema and cretinism clearly indicates that other factors than thyroid insufficiency and pituitary hyperactivity are necessary. Evidence has been reported indicating a definite sex difference in the incidence of thyroidectomy exophthalmos in both man and rabbits and that an increase in the functional activity of the interstitial cells and possibly of the adrenal cortex is necessary. Thyroidectomy with its ensuing increase in sex gland activity, mediated both as a direct gonad-thyroid interrelationship and as an indirect one through the pituitary, and also the parenteral administration of synthetic androgens promote the development of exophthalmos in the rabbit. Gonadectomy abolishes and cryptorchidism maintains an existing exophthalmos in the rabbit. Disturbances in Ca and P metabolism (especially high P and low Ca) affecting neuromuscular irritability appear to be necessary additional factors.

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PHYSIOLOGICAL METHODS IN THE DIAGNOSIS AND TREATMENT OF ASTHMA AND EMPHYSEMA *

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THE purpose of this paper is (1) to describe the diagnostic value of a quantitative and qualitative study of the pulmonary ventilation when employed as a test of respiratory function, (2) to report on the results of physiologically directed therapy in asthma and pulmonary emphysema with especial reference to the evaluation of this treatment by measurements of pulmonary function. For a more general review of the subject, especially the provocative concept of intrinsic lung function, the reader is referred to the recent paper of Miller and Rappaport.[1] The preliminary remarks which we venture are based on our own interpretation of the studies of other investigators and ourselves.

In an attack of asthma the diameter of the small bronchi is reduced at first as a result of spasm of the constrictor muscles. The swiftly elevated negative pressure within the chest, which has become necessary to move air inward against an obstruction, exerts a cupping action on the mucous membrane resulting in congestion and edema of the bronchial wall which further narrows the lumen of the smaller respiratory passageway. Still later, a further development of this physical influence is a sero-mucus which enhances respiratory obstruction until it is coughed up.

A more favorable consequence of the increased negative pressure within the chest during inspiration is the enlargement of the size of the bronchi during this cycle whereas during expiration the lumen of the bronchi suffer relative constriction.[2] To this alteration in pressure during the respiratory cycle may be traced the explanation of the long-drawn out character of expiration in asthma; powerful expiratory efforts result in even greater narrowing of the bronchi and still further delay the egress of air, as will be shown later. Moreover, in severe asthma the quantity of air delivered during the act of exhalation is at times less than that moved *into* the chest, and the alveoli become increasingly distended. Over a long period of time the chest adapts itself to the increased lung volume and assumes its characteristic barrel shape; pulmonary emphysema is the end result.

This type of functional emphysema needs to be sharply distinguished from hypertrophic pulmonary emphysema in which the primary pathogenic factor is a loss of elasticity of the alveolar membrane due to degeneration or infection of the elastic tissue. Some degree of bronchial obstruction is frequently present as an added factor, due to congestion and edema of the bronchial mucous membrane or to spasm of the constrictor muscles, but the

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essential disturbance is an impaired retractility of the lung, with its inevitable train of over-distended alveoli, reduced capillary circulation, increased residual air and limitation in chest movement. As a result of large collections of air residing in portions of the lung which have a functionless alveolar membrane or a deficient blood supply, or a combination of both, an adequate exchange of oxygen and carbon dioxide is imperilled. An increased volume of air movement becomes necessary for the maintenance of this gas exchange; this calls for additional active contraction of the muscles of inspiration and expiration. The consciousness of increased respiratory effort gives rise to the sensation of dyspnea.

In an attack of asthma the sensation of dyspnea takes place immediately upon the recognition of resistance to the free passage of air and the consequent necessity for a greater effort on the part of the respiratory musculature. The heightened negative chest pressures result not only in congestion and edema in the bronchial walls, and in the alveoli as well, but in profound modifications in the circulation. Blood leaves the left ventricle in relatively smaller amounts during the inspiratory cycle, held back by the suction pressure in the lung at this time, and tachycardia and, ultimately, circulatory failure may result. Any procedure which decreases the negative pressure necessary for movement of air past the point of obstruction tends to prevent the pathological changes in the respiratory and circulatory systems. The clinical and experimental evidence for the views here expressed have been reviewed in full too recently to warrant their reproduction in this article.[3]

Methods of Investigation

A quantitative and qualitative study of the pulmonary ventilation has been employed to determine the response of the dyspneic patient to inhalation of various gases. A Benedict-Roth basal metabolism apparatus was used to record graphically the changes in pulmonary ventilation. A high speed drum was connected to the apparatus in order to reveal the qualitative alterations during inspiration and expiration. It is important to employ a motor blower unit to circulate the atmosphere to be tested since the slight resistance produced by breathing through rubber tubing introduces an error in some patients with asthma and pulmonary emphysema. The total pulmonary ventilation was measured by the device reported by Reichert [4] in which a counter is attached to the balance wheel of the metabolism apparatus; this records each inspiration quantitatively and makes possible an immediate calculation of the total pulmonary ventilation at the conclusion of the test. A level respiratory graph and a constant oxygen concentration of the atmosphere being tested was obtained by the use of an apparatus reported by Eckman and Barach [5] in which an automatic feed of oxygen exactly proportional to the patient's requirements is provided. The vital capacity was recorded on both the low and high speed drums in order to

measure it quantitatively and to visualize variations in inspiratory and expiratory velocity.

The amount of air breathed per minute and the form of the respiratory graph were thus graphically recorded. The physiological effects of various types of inhalational therapy could be discerned by comparison with the control graphic records before treatment. The changes resulting from inhalation of helium-oxygen mixtures with and without positive pressure have been shown in previous reports.[6] In this paper the pulmonary ventilation test has been used to illustrate the physiological effects of inhalation of oxygen-enriched air atmospheres in patients with pulmonary emphysema, and the inhalation of vaporized adrenalin and neo-synephrin in patients with asthma and pulmonary emphysema.

The blood gases were measured by the method of Van Slyke and Neill.[7]

Helium-Oxygen Therapy

Helium was proposed as a therapeutic gas in obstructive dyspnea because of its decreased specific gravity in relation to nitrogen.[6] When obstruction exists in the respiratory tubal system, increased pressures become necessary for the movement of air past the point of obstruction. Since the velocity of movement of a gas through constricted orifices is proportional to the square root of the density of the gas the pressure required for the movement of an 80 per cent helium–20 per cent oxygen mixture is almost one-half that required for air. This has been experimentally confirmed in human subjects who breathe through narrow orifices and indicates that a helium-oxygen atmosphere may compensate for approximately a 50 per cent reduction in the normal diameter of the larynx or trachea. When the obstruction is continued in a linear direction throughout the smaller branches of the bronchial tree, the relief obtained by breathing a helium-oxygen mixture is less than when the obstruction is more localized. This is accounted for by the fact that the viscosity of helium is not essentially different from that of nitrogen. The clinical improvement resulting from inhalation of helium-oxygen mixtures has been described in patients with asthma and obstructive lesions in the larynx, trachea and bronchi.[6, 3b] In a series of 105 cases of obstructive dyspnea due to lesions in the upper air passages encountered during anesthesia, Eversole [8] reported that complete relief was obtained in 55 cases, partial relief in 37, with no relief in 13 cases. There were five additional cases in which partial respiratory paralysis occurred during spinal anesthesia. The paralysis was evidenced by absence of intercostal activity and the use of accessory muscles of respiration; the patients themselves found breathing difficult. In all of these cases breathing was said to be much easier when the helium-oxygen mixture was administered than when either air or pure oxygen was given.

The usefulness of helium-oxygen therapy is illustrated in the accompanying table (table 1) in which the clinical state of 13 patients with severe

TABLE I

The Clinical State of Patients with Severe Asthma before and after Helium-Oxygen Therapy

No.	Age	Sex	Duration of Asthmatic History	Probable Etiologic Factors	Clinical State before Treatment	Method Used	Duration of Treatment	Clinical Results
1	43	M.	8 months	Dust	In hospital for five weeks previous to treatment. Responded well to four days filtered air. On removal, patient became worse. Filtered air then gave no relief. For a week previous to helium therapy, patient became progressively worse, finally not responding to adrenalin. Patient comatose and very cyanotic.	Rebreather with mask and mouthpiece—75% helium, 20% oxygen. Intermittent treatments ½ to 2 hours in length, five to nine times daily. 2–3 cm. pressure.	4 days	After five hours of treatment, patient began to respond to adrenalin. Color improved. Complete response to adrenalin established in four days, remained in hospital for eight weeks, then discharged. Readmitted two weeks later, he remained 10 weeks, receiving roentgen-ray therapy. Discharged improved.
2	55	M.	15 years	Bacterial allergy	Two weeks previously, had had left frontal sinusectomy. Severe asthma for following two weeks, receiving injections of adrenalin daily with poor response. Wheezing constantly.	Rebreather with mouthpiece 75% helium, 20% oxygen, 2 cm. pressure. 2–4 half-hour treatments daily.	6 days	Marked subjective and objective relief. Responded to adrenalin after two days treatment with no residual wheeze. Remained in hospital four weeks after helium treatment receiving sinus treatment. On discharge, he was getting 6–10 adrenalin injections daily for residual asthma.
3	35	F.	6 years	Dust	Continuous asthma unrelieved by adrenalin for two weeks.	Rebreather with mouthpiece, 75% helium, 20% oxygen, 2–5 cm. pressure. 3–12 half-hour treatments daily.	6 days	Complete relief from dyspnea. Chest completely cleared in three days. Patient discharged two weeks later without having had any adrenalin, excepting dose on admission, during stay in hospital. Readmitted once again with same result. Remained in hospital for nine weeks for vaccine therapy. Received occasional dose of ephedrine 0/05 gm. per day. Discharged improved. Filter installed at home resulted in almost complete cessation of asthma during following year.
4	62	M.	2–3 years	Pollen dust	Had continuous asthma for 18 hours when admitted to Overnight Ward. During acute attack, he went into a spastic state and stopped breathing. Given 1 ml. of adrenalin and artificial respiration and then began breathing two times per minute. Pulse imperceptible. Appeared to be a hopeless case. Marked acute pulmonary distention.	Helium hood. Helium 70%, oxygen 25%, 3 cm. pressure.	18½ hours	In one-half hour, the patient's respirations were 22 per minute, pulse was strong and regular. Six hours later, patient could be aroused but he still remained in spastic state. Later, patient aroused completely but was irrational at times. Twenty-four hours after start of helium treatment, there was marked improvement. Forty-eight hours later, completely free from asthma and he received no adrenalin during the subsequent two weeks before discharge.
5	57	F.	8 months	Pollen dust	Loss in weight, inability to work, weakness for four weeks preceding admission. Three to four acute attacks of asthma daily with poor response to adrenalin. Residual wheeze after adrenalin.	Helium Rebreather with mouthpiece. Helium 71%, oxygen 23%, ½ to ¾ hour treatments two times daily at 2–3 cm. pressure for 7 days.	7 days	Residual wheeze after adrenalin completely relieved by helium treatment. After two days, patient felt better, slept well, had better appetite and her chest was clear between attacks. Discharged seven days after admission, much improved.

TABLE I—*Continued*

No.	Age	Sex	Duration of Asthmatic History	Probable Etiologic Factors	Clinical State before Treatment	Method Used	Duration of Treatment	Clinical Results
6	61	M.	6 years	Bacterial	An attack of grippe six weeks previous, was followed by asthma which became progressively worse, until patient was taking 1 c.c. adrenalin every hour without relief. Three days before admission, patient coughed up some bronchial casts. Prognosis very poor. Acute pulmonary emphysema.	Helium hood. Helium 70%, oxygen 25%, 3–4 cm. pressure.	3 days 3 hours	Patient experienced subjective relief immediately. Response to adrenalin improved until at end of fourth day complete sensitivity to adrenalin was established. Oxygen by face tent was given for three days and patient was discharged 10 days later, taking 1–2 c.c. adrenalin daily.
7	54	M.	20 years	Bacterial	Long history of asthma and pulmonary emphysema. For four days before admission, patient was in severe intractable asthma receiving no relief from 1 c.c. adrenalin eight times daily. Only slight relief from ½ gr. morphine. Respirations very shallow, 40 per minute, temperature 100.4, pulse 105 very weak. Cyanotic and irrational, unable to void, abdomen distended, condition grave. Acute pulmonary emphysema.	Helium hood. Oxygen 35%, helium 60%, 3 cm. pressure for first three days. Oxygen 35%, helium 60%, 12 hours daily, 100% oxygen 12 hours daily for next four days.	7 days	Patient experienced relief immediately but respiratory rate remained over 30 for three days. On the fourth day, he was removed from helium for 12 hours with recurrence of symptoms. When placed in hood second time, râles in chest disappeared, and patient was removed from apparatus four days later with asthma almost completely gone. Discharged eight days later not having had any morphine or adrenalin in last six days. Completely free from asthma.
8	54	F.	8 months	Bacterial?	Given bladder irrigation—that night fever 104 degrees and severe asthma. Been having severe intractable asthma for four days, no response to adrenalin. Respirations very labored, chest very wheezy.	Helium hood. Helium 70%, oxygen 25%, 3 cm. pressure.	1 day 22 hours	Patient's breathing very much less labored in helium. At end of one day, very much improved reaction to adrenalin. On removal from tent, chest was clear but patient had occasional acute attacks. Six weeks later again developed status asthma—moribund, cyanotic—put in helium O_2 tent with same dosage for one day, 20 hours with marked improvement. She received only 0–0/7 ml. adrenalin daily for following week. In hospital at present for work-up regarding epigastric pains.
9	55	M.	10 years	Bacterial	Admitted from another hospital after one week's stay for severe asthma. Comatose, extremely cyanotic, at times thrashing in bed. Acute pulmonary emphysema.	Helium hood. Helium 73%, oxygen 21%, 3–4 cm. pressure.	16 hours	Chest cleared, breathing easy—no cyanosis in helium atmosphere. After 16 hours in hood, patient was still comatose but with no asthmatic signs. Given oxygen in hood for five days. Mass in abdomen plus tenderness suggested acute cholecystitis. Operation performed with oxygen given continuously. Rectal abscess found (?). Patient died six hours after operation. Post mortem could not be obtained.

TABLE I—*Continued*

No.	Age	Sex	Duration of Asthmatic History	Probable Etiologic Factors	Clinical State before Treatment	Method Used	Duration of Treatment	Clinical Results
10	72	M.	?	Bacterial	Four weeks previous, had dyspnea after bad cough and cold. Two weeks ago, began having continuous asthma unrelieved by adrenalin spray. In hospital five days with continuous asthma. Patient definitely becoming worse.	Helium hood. Helium 71%, oxygen 23%, 3 cm. pressure.	5 days	Gradual improvement during period of treatment. At end of five days, patient given oxygen (50%) by face tent continuously for three days, then periodically during day (1 hr. TID). Comparatively free from asthma, with 1 to 2 injections of adrenalin.
11	52	M.	3 years	Bacterial	Two weeks previously, had antra irrigated. Since that time asthma worse. For last 24 hours, completely refractory to adrenalin. On admission, highly nervous man, chest very wheezy, squeaks and groans can be heard by ear away from chest.	Helium hood. Helium 70%, oxygen 25%.	1 day 15 hours	For first 18 hours, only slight subjective relief experienced. Later complete subjective relief and sensitivity to adrenalin established. On removal from apparatus, only very slight residual wheeze remained which disappeared with 1 c.c. adrenalin. Remained in hospital for two and a half weeks after treatment for sinus checkup and skin tests. No adrenalin given or necessary during that period. Discharged very much improved.
12	14	F.	2½ months	Bacterial	Cold for three days with cough before admission. Severe asthma 24 hours necessitating adrenalin. In hospital for one and a half weeks when her asthma became worse. Temperature 103.8 degrees. Patient gravely ill.	Helium hood. Helium 74%, oxygen 20%, no pressure.	13 hours	Patient's breathing was much easier in helium, but she complained of hood. Very uncoöperative. Technician unable to give gas under pressure. Removed from hood and placed in oxygen tent for two days. Spiking temperature continued for two weeks and then subsided with relief from asthma. Discharged four weeks after admission, very much improved.
13	28	F.	4 months	Bacterial	For three weeks, patient had been having increasingly severe asthma. On admission, she was getting 5 c.c. of adrenalin daily. She was completely refractory to adrenalin, wheezing constantly.	Helium-oxygen rebreather, helium 75%, oxygen 20%, 1–2 cm. pressure for 1–2 hours daily.	3 days	Patient experienced marked subjective relief. Wheeze disappeared on second day and patient had only occasional attack which responded to adrenalin. Two months later, she was readmitted in severe status asthma, cyanosed and dangerously ill. She was treated intermittently for five days about three hours daily and was very much improved. She has had three subsequent admissions with increasingly severe asthma. Her response to helium therapy in each case was very good. In each case, sensitivity to adrenalin was established from within 24 to 48 hours after helium therapy was instigated. At present, she is being treated in the outpatient department with vaccine.

asthma is described before and after treatment. Forty-four patients with severe asthma have been treated, 18 of which were described in earlier reports.[6, 3b] These patients were admitted to the hospital a total of 54 times for urgent dyspnea. In the accompanying table (table 2) they have been divided into three groups.

TABLE II

Response to Helium-Oxygen Therapy in Forty-Four Patients with Asthma

Classification	No. of Admissions to Hospital	Marked Improvement		Moderate Improvement		Little or No Improvement	
		No. of Cases	%	No. of Cases	%	No. of Cases	%
Status asthmaticus	21	14	66	6	28	1	5
Severe more or less continuous asthma	24	10	42	12	50	2	8
Asthma with acute pulmonary emphysema	9	4	44	3	33	2	22
	54	28	52%	21	39%	5	9%

There were 21 admissions for *status asthmaticus*. In this group are included cases in which maximally severe asthma was continuous without any relief resulting from injection of adrenalin. The clinical condition was that of a patient gravely ill. In this group 14 or 66 per cent showed marked improvement incident to the administration of helium-oxygen therapy, generally with positive pressure; 6 or 28 per cent showed moderate improvement, by which we mean that definite objective relief was discerned but that the patient required in addition to other measures a considerable period of time before the asthmatic state was relieved. There was one case in which little or no improvement took place as result of the inhalation of the helium-oxygen mixture for a period of seven hours. In this patient the treatment was temporarily stopped in order to try the effect of intravenous injection of 0.24 gram of aminophyllin in 16 c.c. of normal salt solution. This patient was gravely ill, comatose, deeply under the influence of morphine with a pulse of 140, barely perceptible. During the intravenous injection of aminophyllin the pulse became abruptly impalpable, respiration stopped and the patient died. This patient had been treated four times during the previous two years for *status asthmaticus* of similar severity by the continuous inhalation of helium-oxygen mixtures. Although two to four days of continuous treatment had been necessary at times for complete removal of the asthmatic state, definite clinical relief had ensued within a 24 hour period. It seemed evident that aminophyllin was not suited to this type of advanced *status asthmaticus*.

There were 24 cases of severe, more or less continuous asthma. In this category are included patients who showed some degree of response to

injection of adrenalin but in whom the beneficial broncho-dilating effect was both slight and temporary. In 10 cases or 42 per cent there was marked improvement; in 12 cases or 50 per cent there was moderate improvement; in 2 cases or 8 per cent there was little or no improvement as result of helium-oxygen therapy. It has been emphasized that treatment is directed towards the relief of the chronic wheezing which these patients have; the acute paroxysm is treated by injection of adrenalin when it is effective. More recently, inhalation of large amounts of vaporized adrenalin and neo-synephrin has been used.

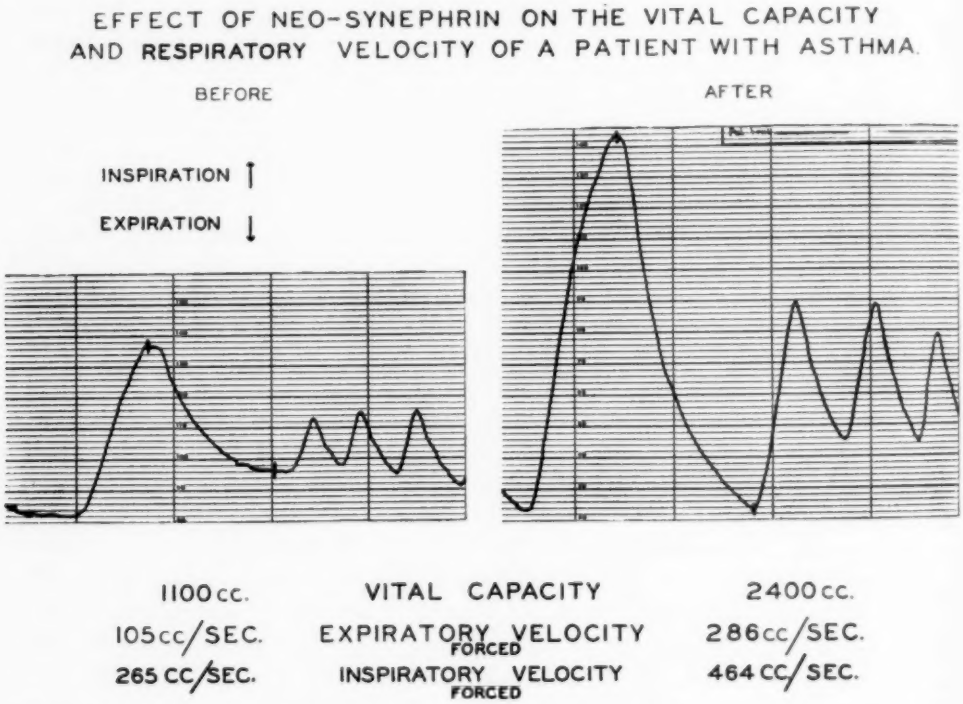
There were nine patients in whom severe asthma was accompanied by acute pulmonary emphysema. In these cases the lungs were distended, the respiratory rate was increased and the breathing was shallow. Four showed marked improvement, three moderate improvement and two little or no benefit.

Of the total 54 admissions to the hospital 28 or 56 per cent showed marked improvement, 21 or 42 per cent showed moderate improvement and 5 or 10 per cent showed little or no improvement. In those who showed little benefit, the poor response to helium-oxygen therapy may be attributed either to the severity of the obstruction or to the fact that the slight degree of relief obtained resulted in poor coöperation from the patient.

Inhalation of the Vapor of Neo-Synephrin and Adrenalin

The introduction of a nebulizer with the vaporization of 1–100 adrenalin by Graeser and Rowe [9] made it possible for many patients to terminate asthmatic dyspnea without the use of a hypodermic injection. In many instances squeezing the rubber bulb five times terminates a mild or moderate seizure. In other cases slight, temporary or no relief is obtained. Measurement of the amount of adrenalin ordinarily vaporized shows that it is about 0.01 c.c. In the more severe cases of asthmatic dyspnea we have found that the vaporization of 1 to 2 c.c. of 1–100 adrenalin has afforded relief when the smaller dosage was ineffective. In order to vaporize this amount of adrenalin we have employed the current of air from a compressed air tank or from an oxygen tank at a flow of 8 liters per minute. The lower end of the nebulizer is connected by a rubber tube to the outlet of the oxygen regulator. A small pump capable of maintaining a pressure of 5 to 10 lbs. has also been used.[9] During the period of 7 to 15 minutes the patient holds the upper end of the nebulizer in his mouth and breathes in the ordinary manner except that it is generally preferable to have the nose closed in order that as much of the vapor as possible be inhaled. We have found no tremor, nervousness or elevation of pulse rate or blood pressure in over 20 patients who inhaled 1.0 c.c. of 1–100 adrenalin, although it is entirely probable that patients sensitive to adrenalin may show the characteristic symptoms induced by hypodermic injection of smaller dosage of adrenalin.

Richards, Barach, Cromwell and Darling have introduced the inhalation of 1 per cent neo-synephrin, used in the same manner as 1–100 adrenalin (to be reported in full later). Since the instillation of neo-synephrin on swollen nasal mucous membrane is effective in reducing the congestion over a period of three hours without the secondary swelling so characteristic from local application of adrenalin,[11] it seemed likely that inhaling the vapor of this drug would result in a similar effect on the bronchial mucous membrane. The markedly decreased toxicity of this drug in comparison with either adrenalin or ephedrin seemed an additional value. The broncho-dilator



GRAPH 1. Effect of neo-synephrin on the vital capacity and respiratory velocity of a patient with asthma.

effect on patients with asthma is much less marked than that accomplished by adrenalin. We have employed from 1 to 3 c.c. of a 1 per cent watery solution of neo-synephrin in vapor form in a series of 20 patients without noticeable effect on the pulse or blood pressure.[10] Since the drug has been found valuable in shock, slowing the pulse rate and raising the blood pressure in this condition,[12] its use in severe asthma would have this special advantage.

In the accompanying graph (graph 1) the effect of inhaling 1 c.c. of 1 per cent neo-synephrin is shown in a patient with severe asthma and acute functional emphysema. It will be observed that both inspiration and expiration were markedly prolonged during forced respiration. The expira-

tory velocity increased from 105 c.c. per second before inhalation of neo-synephrin to 286 c.c. per second after. The inspiratory velocity increased from 265 c.c. to 464 c.c. The vital capacity was more than doubled, increasing from 1100 c.c. to 2400 c.c. This response was not obtained with all patients. In the succeeding graph obtained in a similar patient (graph 2) response to inhalation of 1 c.c. of 1–100 adrenalin is revealed. It will be observed that a similar increase in inspiratory and expiratory velocity has taken place, but with a very slight increase in vital capacity. The change in the form of the graph is comparable to that produced by neo-synephrin. In most cases, the relief obtained from adrenalin (1–100) is greater than that provided by 1 per cent neo-synephrin.

In patients with pulmonary emphysema we have employed neo-synephrin in 1 or 2 c.c. doses, night and morning, in order to increase the available functional air by diminishing bronchial obstruction due to congestion or edema. In those cases in which some degree of bronchial spasm is present it has been found valuable to use equal parts of 1–100 adrenalin and 1 per cent neo-synephrin. Frequently relief is obtained within 1 minute of inhalation of the combined drugs but it is our impression that the improvement is more lasting when a full c.c. of the mixture is employed. In addition to daily inhalation of neo-synephrin morning and evening it has been used before the patient undertakes any unusual exertion. The opening up of the bronchial passageway which is induced in most instances allows for greater exertion with less dyspnea.

Inhalation of Oxygen

Inhalation of oxygen-enriched air in concentration of 40 to 50 per cent has been found useful in the treatment of more or less continuous asthmatic dyspnea. The arterial anoxemia is at least partially relieved and there is evidence that a decreased pulmonary ventilation takes place.[13] In a number of graphic studies of acute asthma which we have made, the change in pulmonary ventilation incident to the inhalation of oxygen-enriched air has been either slight or absent. Nevertheless, continuous oxygen therapy for one or two weeks has frequently been followed by cessation of a previously severe protracted asthma.

In chronic hypertrophic pulmonary emphysema a reduced oxygen saturation of the arterial blood is frequently although not always present. Dyspnea on exertion is the earliest characteristic symptom. As the disease progresses these patients become incapacitated and suffer from severe dyspnea at rest. The mechanics of the respiratory act in patients with this disease has been subjected to intensive study.[14] The muscles of inspiration are already in the inspiratory position when the act of inspiration begins. An increased amount of work becomes necessary to further distend the lung and a large portion of the air that is inhaled is segregated in peripheral alveolar sacs having an atrophic membrane without an adequate capillary

circulation. As a result partially oxygenated blood is contributed to the aortic stream, and anoxemia and increased CO_2 tensions of the arterial blood are often found. There is a corresponding increase in the alkali reserve. Due to the loss of elasticity of the pulmonary membrane the lungs do not passively collapse and an active expiratory effort is required. As a result of progressive distention of the lungs, the diaphragm is flattened and its contraction pulls the costal margins inward instead of increasing the lung volume at the base of the lung. The upper intercostal muscles, the sterno-cleido-mastoid and the scalene muscles move the chest upward and in a slightly anterior position. Pulmonary ventilation mainly manifests itself as upper costal respiration, the diaphragm contributing less and less. A large increase in residual air and a decreased vital capacity regularly take place.

The result of these mechanical difficulties and of the pathological state of the pulmonary tissue itself is an impairment of the primary function of the lung, namely, the exchange of the blood gases between the blood and the alveolar air. The lack of correspondence between the degree of anoxemia and the intensity of dyspnea does not make less important the humoral factor as a cause of dyspnea in the emphysematous patient. The sensitiveness to oxygen-want varies considerably in these patients. In 10 patients with severe pulmonary emphysema who frequently experienced dyspnea at rest the inhalation of oxygen increased subjective comfort and diminished the objectively perceived labored breathing in each instance. In all these patients oxygen treatment had been carried on for at least one week and in most of them for considerably longer periods (data to be presented below). In certain cases relief of dyspnea came on immediately, in others after a period of three to five days of inhalation of 40 to 50 per cent oxygen. We have selected two patients who have been treated over a long period of time to illustrate the crucial rôle played by the chemical factor in the cause of dyspnea. The clinical improvement that results from continuous oxygen therapy in this disease has been noted previously,[15] but an adequate recognition of the therapeutic importance of oxygen treatment has not been generally understood. It is our purpose to show that the physiological response to inhalation of oxygen enriched atmospheres reveals that the primary cause of the labored breathing is directly related to the impaired function of the lung in respect to exchange of blood gases. We believe that the emphasis on proprioceptive reflexes as a cause of this type of dyspnea has unduly minimized the humoral chemical influence.

Case Reports

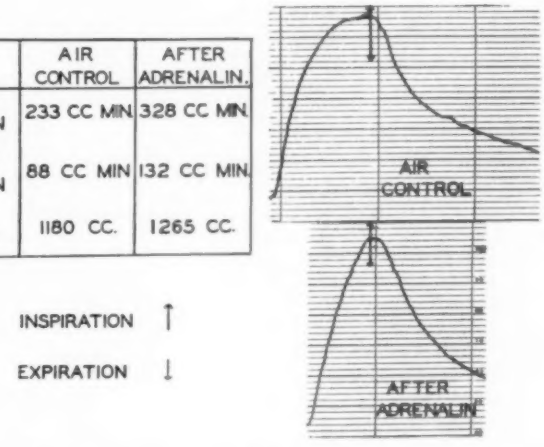
Case 1. Male, aged 74 years. Admission to hospital, September 2, 1937. Present illness: Following a protracted acute bronchitis the patient developed progressively severe dyspnea. During the past year the slightest exertion, such as standing for five minutes, eating, or bathing resulted in severe shortness of breath and heart pounding. After awakening in the morning he had a paroxysmal attack of dyspnea which lasted two to four hours, leaving him exhausted, with a gradual

recovery in the late afternoon. *On examination* he was a tall, well built man. The dyspnea was characteristically that of a patient with hypertrophic emphysema. There was an elevation of the upper chest with contraction of the neck muscles; the lower costal margin and the infra-sternal region were drawn inward. The lungs were hyper-resonant, breath sounds were prolonged; there were a moderate number of wheezing râles. The heart was not enlarged; the rate was 105 to 120; the blood pressure was 142 systolic and 100 diastolic. Hemoglobin 98 per cent (100 per cent equals 14.9 grams); red blood cells 4 million. Venous pressure 85 with a rise of 4 cm. on expiration. Roentgen-ray of the chest showed a moderately flattened diaphragm with an essentially normal cardiac shadow except for a slight widening of the aortic arch; he did not appear cyanotic.

On September 5, 1937, an analysis of the arterial blood gases showed an oxygen saturation of 92.9 per cent and a CO_2 content of 51.9 volumes per cent. At this time numerous graphic records were obtained of the pulmonary ventilation during

EFFECT OF 1:100 ADRENALIN ON THE VITAL CAPACITY AND RESPIRATORY VELOCITY IN A PATIENT WITH ASTHMA AND ACUTE PULMONARY EMPHYSEMA.

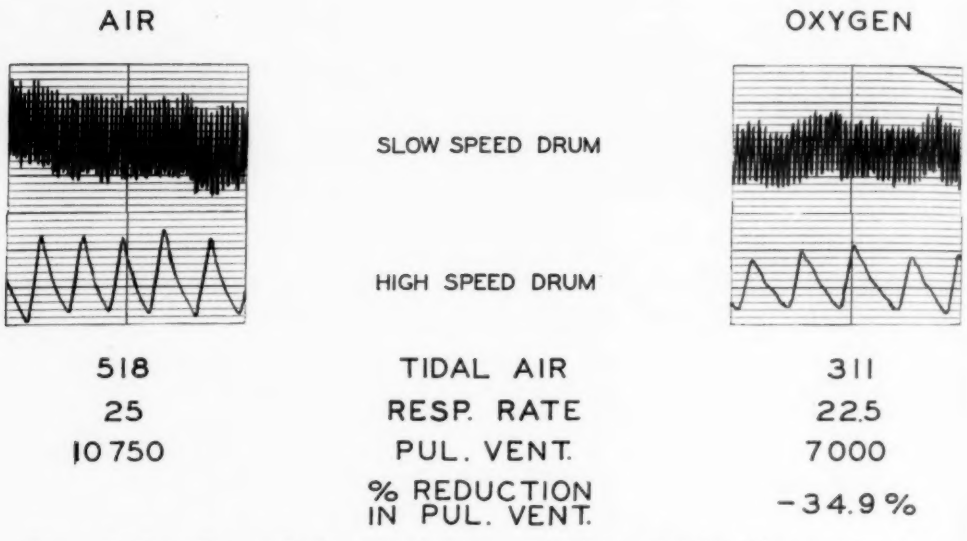
	AIR CONTROL	AFTER ADRENALIN.
VELOCITY INSPIRATION	233 CC MIN.	328 CC MIN.
VELOCITY EXPIRATION	88 CC MIN.	132 CC MIN.
VITAL CAPACITY	1180 CC.	1265 CC.



GRAPH 2. Effect of 1:100 adrenalin on the vital capacity and respiratory velocity in a patient with asthma and acute pulmonary emphysema.

inhalation of air and 100 per cent oxygen. In the accompanying graph (graph 3) a characteristic result is shown. It will be observed that there was an immediate reduction in pulmonary ventilation of 34.9 per cent incident to the inhalation of oxygen, due in part to a fall in respiratory rate from 25 to 22.5 and in part to a decrease in the volume of the tidal air from 418 to 211 c.c. It is noteworthy that this marked decrease in the ventilatory requirement took place in the presence of a very slight lowering of the arterial oxygen saturation. There was definite consciousness of relief of dyspnea. Oxygen treatment begun at this time, consisted of residence in a portable oxygen room at his home for approximately 17 hours during the 24, including, for the most part, the evening, night and early morning. There were five periods in which for 10 days to 3 weeks the patient resided continuously in the oxygen chamber at the hospital. Up to February 15, 1938 the oxygen concentration employed was 50 per cent; from then on up to the date of writing (March 25, 1938) it has been between 37 and 40 per cent.

IMMEDIATE REDUCTION IN PULMONARY VENTILATION, WHEN BREATHING OXYGEN, IN A PATIENT WITH PULMONARY EMPHYSEMA .



GRAPH 3. Immediate reduction in pulmonary ventilation, when breathing oxygen, in a patient with pulmonary emphysema.

During the hospital admissions the patient was removed from the oxygen room for periods of 1 to 17 hours in order to test his ventilatory response to inhalation of air and 100 per cent oxygen. The results on the pulmonary ventilation are shown in the accompanying table (table 3). In 14 tests during a period of six months, a

TABLE III

Immediate Reduction in Pulmonary Ventilation on Inhaling 100% Oxygen, in a Patient with Pulmonary Emphysema, during a Course of Oxygen Treatment

Date	Tidal Air	Air 100% O_2	Resp. Air	Rate 100% O_2	Pulmonary Ventilation Liters per min.		% Reduction in Pulm. Vent. due to Oxygen	Vital Capacity	Relation to Course of Oxygen Treatment
					Air	100% O_2			
9- 3-37	390	216	29.5	30	11500	6480	43.7		Before O_2 treatment
9- 5-37	304	270	26.5	26.5	8660	7180	17.1		" " "
9- 8-37	419	375	25	25	10470	9380	10.4		O_2 treatment 3 days
9-14-37	363	305	25	24.5	9080	7470	17.7	1430	" " 9 "
10-26-37	352	296	25.5	21	8970	6220	30.7	1630	" " 51 "
10-29-37	358	265	25	23	8940	6090	31.9		" " 54 "
11-24-37	518	311	25	22.5	10750	7000	34.9	1490	" " 80 "
12-22-37	370	320	27	24	9980	7680	23.0	1535	" " 108 "
12-27-37	360	285	24	20.5	8640	5840	32.4		" " 113 "
1-17-38	320	188	24	23	7690	4320	43.8	1660	" " 137 "
1-20-38	369	286	24	22	8860	6290	29.0	1880	" " 140 "
1-30-38	408	321	23	21	9370	6740	28.1	1680	" " 150 "
2- 4-38					9290			1980	" " 155 "
3- 4-38					9810	7432	21.5		" " 183 "
3-10-38					7860			2125	" " 189 "
3-23-38	415	338	19.5	19	8100	6420	20.7		" " 202 "

decrease in pulmonary ventilation of from 20 to 40 per cent took place when 100 per cent oxygen was substituted for air, in each instance with an immediate consciousness of alleviation of dyspnea. When the patient breathed a 37 per cent oxygen atmosphere the immediate reduction in pulmonary ventilation was found to be 17 per cent. On January 17, 1938 the patient had been in air for six hours prior to the test. At that time his arterial oxygen saturation was 98.8 per cent. The measurement of his ventilation even in the absence of arterial anoxemia showed a fall of 43.8 per cent. The finding, therefore, of a normal or slightly lowered arterial oxygen saturation in a dyspneic patient does not warrant the assumption that the oxygen tension in the blood is not causally related to dyspnea. It is evident from the numerous observations on this patient that the excessive resting pulmonary ventilation, although it produced dyspnea, maintained a normal or nearly normal oxygen saturation of the arterial blood.

The vital capacity of this patient at the beginning of treatment was 1430 c.c. At the date of writing (March 13, 1938) the vital capacity is 2125 c.c.; this is further increased after inhalation of 2 c.c. of 1 per cent neo-synephrin to 2300 c.c. It may be mentioned at this point that two weeks after initiation of oxygen treatment all râles cleared in the lungs and the patient has not been conscious of a wheeze at any time.

The arterial oxygen saturation when the patient was in an atmosphere of 40–50 per cent oxygen was raised above the normal range, indicating that the hemoglobin was fully saturated and that there was additional oxygen in physical solution in the plasma (table 4). The carbon dioxide content of the arterial blood was 51.9 volumes per cent in air, when his pulmonary ventilation was much increased. After four months of intermittent oxygen treatment (17 hours in 24) the arterial CO_2 content in air was 63.1 volumes per cent. During a period of continuous residence in atmosphere of 50 per cent oxygen in the hospital from January 17 to February 1, 1938 the CO_2 content rose from 63.1 volumes per cent to 78.6 volumes per cent on January 21 and then subsequently declined on January 28 to 65.8 volumes per cent. On February 1 the CO_2 content was 66.9 volumes per cent. On March 23, 1938, the arterial CO_2 content breathing air was 59.8 volumes per cent. The alteration in CO_2 content due to oxygen treatment will be discussed later. (Table 4.)

After six months of oxygen treatment, for the most part for a period of approximately 17 hours a day, the patient presents a clinical state decidedly better

TABLE IV

Blood Cases in a Patient with Pulmonary Emphysema during Oxygen Treatment

Date	Oxygen Content Vol. %	Oxygen Capacity Vol. %	Oxygen Saturation %	CO_2 Content Vol. %	Remarks
9– 3–37	20.15	21.7	92.9	51.9	Before oxygen treatment
9–22–37	16.9	18.6	91.0	61.6	Breathing air
9–22–37	19.3	19.6	99.0	63.8	Breathing 50% oxygen
1–17–38	16.6	16.8	98.8	63.1	Breathing air, after 137 days oxygen treatment
1–18–38	18.4	17.9	102.8	69.9	Breathing 50% oxygen
1–21–38	17.8	17.55	101.5	78.6	Breathing 50% oxygen, after 141 days oxygen treatment
1–28–38	17.45	16.95	102.9	65.8	Breathing 40% oxygen, after 148 days oxygen treatment
2 –1–38		17.1		66.95	Breathing 40% oxygen, after 152 days oxygen treatment
3–23–38	15.55	16.9	92.0	59.85	Breathing air, after 202 days oxygen treatment.

than that prior to treatment. He has no morning attacks of dyspnea. The inhalation of 0.5 c.c. of 1–100 adrenalin followed two hours later by the inhalation of 1 c.c. of neo-synephrin enables him to bathe, and to get dressed without uncomfortable dyspnea. Although a wheel chair is made use of to cover any extended distance he is able to walk 60 steps to and from the dining room or into the living room without undue puffing. It is also possible for him to go to a hotel for dinner and to entertain friends. His pulse rate has decreased from a range of 105–120 to a range of 80–100. His most recent test showed a pulmonary ventilation of 8.1 liters per minute in air, which is considerably less than his pulmonary ventilation before oxygen treatment was begun. There is a marked decrease in infra-sternal and lower intercostal retraction during the residence in the oxygen-enriched atmosphere.

Oxygen treatment in this patient has resulted in a marked relief of subjective dyspnea and a distinct improvement in the function of the respiratory system. It seems likely that the progress of the disease has been retarded.*

Case 2. Male, aged 59. Admission to hospital February 20, 1936. Present illness: The patient has had chronic dry hacking cough for 40 years. Seven years ago he began to have attacks of definite bronchitis lasting two to three days, occurring two to three times a year, accompanied by fever and sputum. Following removal of his gall-bladder at that time and the development of a ventral hernia, dyspnea on exertion began. A gradual increase of severity of dyspnea took place so that during the past year it has become impossible for him to walk 40 yards. In addition, he developed paroxysms of extremely labored breathing which occurred at night without relation to exertion. On two occasions he inhaled 50 per cent oxygen for one to two hours without relief. At the time of our first observation, he had an almost continuous hacking cough; the slightest effort caused extreme dyspnea, he was weak and depressed. *On examination,* he was a thin, poorly developed man of 56 years, bending forward, whether standing or sitting, markedly dyspneic with upper costal respiration, inspiratory contraction of the neck muscles and retraction of the lower intercostal and substernal regions. There was no cyanosis. The lungs were hyperresonant, breath sound feeble and prolonged without râles. Roentgen-ray of the chest showed a markedly flattened diaphragm with a long narrow heart. The pulse rate was 80; the blood pressure was 120 systolic and 70 diastolic. Venous pressure 40. The lung fields showed evidence of fibrotic change especially in the lower regions. An abdominal binder had occasionally been worn without noticeable change in his breathing, and without subjective relief.

The patient was too dyspneic to measure his pulmonary ventilation with a mouthpiece and nose clip; a Benedict helmet respiration apparatus [16] was therefore used which gives a pulmonary ventilation about 15 per cent less than that obtained with the mouthpiece due to an unrecorded fluctuation in the rubber collar during the respiratory cycle. Under these circumstances the pulmonary ventilation in air was 5.7 liters and in 100 per cent oxygen 4.8 liters per minute. The decrease in pulmonary ventilation was due entirely to a lowering of the tidal air from 309 to 209 c.c.

In a later admission (December 23, 1936) his arterial oxygen saturation in air was 96.7 per cent; the CO_2 content was 66.3 volumes per cent. On the following day breathing 40 per cent oxygen in the oxygen room the arterial oxygen saturation was 102.7 per cent; the CO_2 content 71.8 volumes per cent. The next day the CO_2 content was 74.1 volumes per cent and four days later with the same oxygen concentration in the room 70.8 volumes per cent. During the period of residence in the oxygen room the patient had only a transient sensation of dyspnea; he only infre-

* At the time proof was received, September 4, 1938, one year after institution of oxygen treatment and inhalation of adrenalin-neo-synephrin vapor, the patient continues to maintain the improvement described, both clinically and in respect to measurements of pulmonary function.

quently felt the inclination to use inhalations of 1–100 adrenalin and he had no severe paroxysms of dyspnea. On his return home his dyspnea again increased, despite nasal oxygen at three liters per minute, and was only relieved completely in an atmosphere of 100 per cent oxygen. At night nasal oxygen was successful in permitting sleep without continual coughing or dyspnea. Paroxysmal attacks of dyspnea were relieved by inhalation of 1–100 adrenalin.

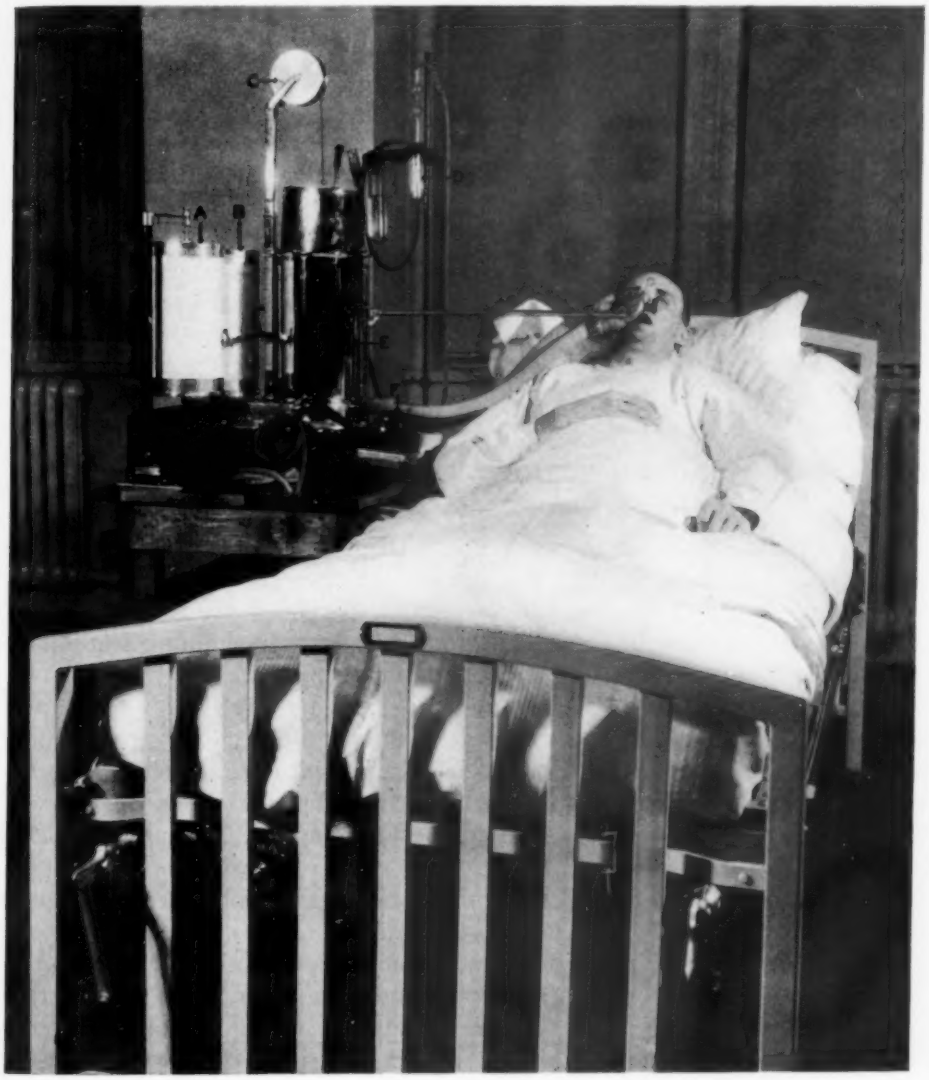


FIG. 1. *A*. High speed drum. *B*. Standard recording drum. *C*. Reichert counter. *D*. Levelling device with automatic oxygen administration. *E*. Spirometer of basal metabolism apparatus. *F*. Motor blower unit with rheostat.

During the first year of oxygen treatment the patient was able to do four to five hours legal work at his office each day. During the second year his failure to improve sufficiently to restore his customary earning power contributed largely to an

increasing depression. Even during period when his dyspnea was largely controlled by continuous oxygen therapy at the hospital, he retained a gloomy outlook based on the realization of his loss of earning power and, finally, on his inability to afford adequate oxygen therapy at home.

The intermittent employment of oxygen therapy in this patient has prolonged life over a two year period. The paroxysmal dyspnea, the cough and the more continuous labored breathing largely disappeared in continuous residence in 40 to 50 per cent oxygen in a hospital oxygen room. These symptoms recurred at home and are now only partially relieved by nasal oxygen plus inhalations of adrenalin and neo-synephrin. The depression which the patient had at the onset of treatment was considerably improved during the first year in which he was able to work part of the day. If the economic situation in which he finds himself were less precarious than it is, his depression would undoubtedly be materially modified. He is unable to do without nasal oxygen, three liters per minute, although this is inadequate to prevent dyspnea. Cessation of oxygen treatment, however, results in return of cough and severe dyspnea. This patient illustrates the importance of considering the factor of expense in arranging for long continued treatment of a patient with emphysema. In individuals who are not able to afford prolonged oxygen treatment the decision to provide temporary relief should be seriously weighed. Removal from an oxygen-enriched atmosphere may result in a recurrence of dyspnea, cough and depression, which may become difficult to handle.

Comment on Oxygen Treatment and Pathological Physiology in Patients with Pulmonary Emphysema

Graphic records of the pulmonary ventilation in patients with pulmonary emphysema have been used to elucidate certain aspects of the pathological physiology of the disease and to serve as a basis for treatment. In the two cases selected for detailed description the resting pulmonary ventilation was markedly increased above normal. In each instance, the inhalation of 100 per cent oxygen for a five minute test period resulted in a substantial lowering of the total pulmonary ventilation and in partial relief of subjective dyspnea. Residence in an oxygen chamber with an oxygen concentration of 40 to 50 per cent was followed by complete relief of dyspnea in one case at the end of four days and in the other after 24 hours treatment. Determination of the arterial oxygen saturation revealed in both instances a slightly lowered oxygen saturation. While the patient was breathing 50 per cent oxygen the arterial oxygen saturation was increased above the usual normal range. It may be pointed out, therefore, that a normal saturation of the arterial blood with oxygen cannot be used as an argument that dyspnea is not causally related to the oxygen tension of the blood and tissues. In the two patients studied, one over a period of two years and the other for six months, it was clear that an excessive pulmonary ventilation was maintained at the expense of subjective dyspnea, but with the result that a normal or nearly normal oxygen saturation of the arterial blood was achieved. Since complete freedom from dyspnea took place in an oxygen enriched atmosphere, it is difficult to avoid the conclusion that their pulmonary ventilation in air had been increased to avert anoxemia. Expressed from a more objective point of view, these patients consistently revealed a

sensitiveness to the oxygen tension in the atmosphere which determined the quantity of air moved in and out of the lungs; increasing the oxygen supply was followed by relief of dyspnea, decreasing the oxygen supply resulted in recurrence of dyspnea.

Proprioceptive reflexes from the lungs and the chest wall are responsible for the transmission intracerebrally of the sensation of dyspnea. The mechanical difficulties of breathing which are in large part created as a result of chronic over-distention of the lungs, bring about a patho-physiological state in which the patient's resting pulmonary ventilation is nearer to his maximal pulmonary ventilation than is the case in the normal individual. The degree of dyspnea in chronic pulmonary disease has been said to vary directly with the extent to which the pulmonary ventilation approaches the maximal pulmonary ventilation or to the vital capacity.[14] In the patients which we have studied this correlation undoubtedly exists but we have been particularly impressed with the rôle played by the primary function of the lung, namely, the transmission of oxygen into the arterial blood. The increased respiratory effort which is perceived as labored breathing tends to maintain a constancy of the internal environment in respect to tissue oxygen supply.

In patients with chronic pulmonary disease treated over relatively long periods of time with oxygen-enriched atmospheres, a characteristic rise in the carbon dioxide content of the arterial blood takes place. In previous reports by Richards and the author,[17] this has been explained as a mechanism which allows a greater elimination of CO_2 per breath in the presence of a decreased pulmonary ventilation initially made possible by an increase in the oxygen tension of the arterial blood. A progressive rise in arterial CO_2 content has been observed in patients with chronic heart disease, occurring in conjunction with a lowering of the total pulmonary ventilation. The elevation in arterial CO_2 content may reach a maximum in some cases in two to three weeks and then gradually fall toward the normal level even during continuous residence in an oxygen-enriched atmosphere. This type of response has been characteristic of patients who have shown clinical improvement in respect to pulmonary pathology and function. In patients with chronic pulmonary disease in whom clinical improvement has persisted after removal from an oxygen environment a similar response has been observed, namely, a decline in CO_2 content following an initial rise. Thus, the first case reported in this paper had a substantial lowering of arterial CO_2 content following a preliminary rise, and clinically experienced marked benefit; the second case showed only a slight fall in arterial CO_2 content from his maximal rise, and clinically his symptoms recurred after removal from an oxygen environment.

In the accompanying table (table 5) the maximal rise in arterial CO_2 content in 10 patients with chronic pulmonary disease treated with oxygen is recorded. In Case 2 a negligible increase in CO_2 content was found. In this patient despite active tuberculosis there was little or no impairment

of respiratory function in respect to absorption of oxygen. In seven of the remaining patients, the CO_2 content of the arterial blood rose 20 or more volumes per cent. In Case 3 an arterial CO_2 content of 132.1 volumes per cent was found after six months residence in an oxygen enriched atmosphere. In this patient an advancing pulmonary fibrosis, associated with infection or carcinoma, progressively impaired pulmonary function in respect to the absorption of oxygen. Although she was at first comfortable in an atmosphere of 40 per cent oxygen, she later required 60 per cent oxygen. Her vital capacity at that time appeared to be no greater than 250 c.c. It may be concluded that a progressive elevation in the carbon

TABLE V

Maximal Rise in Arterial CO_2 Content in 10 Patients with Chronic Pulmonary Disease Treated with Oxygen

Case Diagnosis No.	Arterial Oxygen Saturation %		Arterial CO_2 Content		Remarks
	before Treatment	after Treatment	before Treatment	after Treatment	
1. Chronic pulmonary tuberculosis	88%	93%	54.9	73.5	Patient resided in oxygen chamber, 50% oxygen for 43 days at time of second test
2. Chronic pulmonary tuberculosis	97%	95%	49.0	51.0	Patient resided in oxygen chamber, 50% oxygen 7 days at time of second test.
3. Advanced pulmonary fibrosis		89%		132.1	Test obtained after 6 months residence in oxygen chamber; oxygen concentration between 50–60%.
4. Advanced pulmonary fibrosis	70%	90%	38.4	69.7	Patient resided in oxygen chamber at 50% oxygen 4 days at time of test.
5. Pulmonary emphysema	92.9%	101.5%	51.9	78.6	Six months oxygen treatment, 17 hours daily. Two weeks before test continuous residence in 50% oxygen.
6. Pulmonary emphysema	68.09%	93.0%	62.6	91.7	1 month in 50% oxygen.
7. Pulmonary fibrosis	86.0%	96.0%	66.0	84.2	6 days in 45% oxygen.
8. Pulmonary fibrosis and emphysema	96.7%	102.7%	66.3	74.1	6 days in 40% oxygen.
9. Chronic pulmonary tuberculosis and pulmonary fibrosis	88.0%	100.0%	57.0	77.0	35 days in 45% oxygen.
10. Pulmonary fibrosis and emphysema	93.0%	97%	60.0	66.2	5 days at 26% oxygen.

dioxide content of the arterial blood during continuous oxygen treatment indicates a failure of improvement both in pulmonary pathology and function, whereas a fall in arterial CO_2 content following a previous rise is of favorable prognostic import and indicates a likelihood of betterment in pulmonary function and clinical improvement as result of oxygen treatment.

The inhalation of 100 per cent oxygen does not always show an immediate fall in pulmonary ventilation in patients with pulmonary emphysema. This response is sometimes obscured by the factor of respiratory obstruction due to spasm of the bronchial musculature and the congestion and edema of the bronchial wall. When bronchial obstruction is removed by inhalation of 1–100 adrenalin, 1 per cent neo-synephrin or a combination of both,

the patient may then show a marked decrease in pulmonary ventilation due to inhalation of 100 per cent oxygen, although little or no effect was produced by oxygen prior to inhalation of these substances. Thus, in a patient with severe pulmonary fibrosis who is now experiencing considerable benefit from continuous oxygen therapy, the pulmonary ventilation test at first showed very slight alteration when oxygen was substituted for air. However, when the factor of bronchial obstruction was removed by inhalation of adrenalin and neo-synephrin a marked diminution in the amount of air breathed per minute took place. In the accompanying table (table 6) the pulmonary ventilation test is recorded before and after inhalation of adrenalin and neo-synephrin. In six out of eight tests the diminution in pulmonary ventilation when 100 per cent oxygen was breathed was much

TABLE VI

Reduction in Pulmonary Ventilation When Oxygen Is Substituted for Air in a Patient with Pulmonary Emphysema before and after Inhalation of Vaporized Adrenalin and Neo-Synephrin

Inhalent	Before Inhalent			After Inhalent		
	Pul. Vent. Air	Pul. Vent. Oxygen	% Reduction in Pul. Vent.	Pul. Vent. Air	Pul. Vent. Oxygen	% Reduction in Pul. Vent.
	c.c. per min.			c.c. per min.		
3 c.c. Neo-synephrin 1 c.c. 1 : 100 adrenalin	10200	9330	8.7	10900	8560	21.5
3 c.c. Neo-synephrin 1.5 c.c. 1 : 100 adren.	11300	9200	18.6	15460	9120	41.0
3 c.c. Neo-synephrin 1 c.c. 1 : 100 adrenalin	8820	8295	6.0	10850	6600	39.2
3 c.c. Neo-synephrin	7110	8120	10.9	8300	7950	5.4
2 c.c. Neo-synephrin	11400	9160	19.7	11500	8380	27.1
2 c.c. Neo-synephrin	10930	9010	17.7	9500	8210	13.6
1 c.c. 1 : 100 adrenalin	10070	9550	5.2	10800	8700	19.4
1 c.c. 1 : 100 adrenalin	11100	10110	8.9	11400	8720	23.5

greater after inhalation of adrenalin and neo-synephrin. Thus, in the third test, inhalation of 100 per cent oxygen was followed by a 6 per cent reduction in pulmonary ventilation; after inhalation of 3 c.c. of neo-synephrin and 1 c.c. of 1–100 adrenalin there was a 39 per cent reduction in pulmonary ventilation when 100 per cent oxygen was breathed. It is evident, therefore, that the factor of respiratory obstruction should be counteracted by inhaling the vapor of adrenalin and neo-synephrin before it is concluded that 100 per cent oxygen does not lower the total pulmonary ventilation. It should also be remembered that the patient with chronic pulmonary disease may show a gradual decrease in labored breathing in a period of three to five days even when the pulmonary ventilation test shows no immediate decrease in the volume of air breathed with oxygen.

The importance of the chemical factor in the etiology of dyspnea in patients with pulmonary emphysema is illustrated in the following experiment performed on the first case reported above. The pulmonary ventilation was determined while he was breathing air. Arterial blood was taken for measurement of the blood gases and the pH. The patient then inhaled 100 per cent oxygen, and arterial blood was drawn 90 seconds later. The data are recorded in the accompanying table (table 7). It will be

TABLE VII

Pulmonary Ventilation and Blood Gases of a Patient with Pulmonary Emphysema, before and after Relief of Dyspnea Due to Inhalation of 100% Oxygen for 90 Seconds

Breathing Air		After Breathing 100% Oxygen for 90 Sec.
8100 c.c.	Pulmonary ventilation	6420 c.c.
92.0%	Arterial oxygen sat.	101.2%
59.85 Vol. %	CO_2 content	60.75 Vol. %
57.2 Vol. % *	CO_2 capacity	57.35 Vol. % †
7.41	pH	7.40

* Equilibrated at 43.7 mm. Hg pressure CO_2.
† Equilibrated at 45.2 mm. Hg pressure CO_2.

observed that an immediate fall in pulmonary ventilation from 8100 to 6420 c.c. took place coincident with a rise in arterial oxygen saturation from 92.0 to 101.2 per cent. The CO_2 content of the arterial blood rose slightly and the pH changed merely from 7.41 to 7.40. A more comprehensive study of variations in CO_2 tensions and in pH of the arterial blood as they are affected by oxygen treatment has been made by D. W. Richards,[18] but it is sufficient for our present purpose to indicate that the change in oxygen saturation of the arterial blood was essentially responsible for the decline in pulmonary ventilation and the concomitant alleviation of dyspnea. The time interval involved, namely 90 seconds, was too brief to allow any change to take place in the mechanical difficulties of breathing. Although we are aware that relief of labored breathing does not take place as promptly as it did in this instance in all cases of pulmonary emphysema, it is nevertheless our belief that continuous residence over a period of three to six days in an oxygen enriched atmosphere will result in a marked decrease of labored breathing in most instances.

POSITIVE PRESSURE BREATHING

Atmospheres under small increases of pressure such as 2 to 5 cm. of water have been employed in inhalational therapy in order to diminish the inspiratory effort and to facilitate the egress of air during expiration by diminishing expiratory constriction of the intra-thoracic bronchi and bronchioles.[6f, 3] A study has been made in collaboration with Dr. Paul Swenson in which the size of the smaller bronchi has been measured before and after positive pressure was used. (A full report will be published elsewhere.)

Patients during an attack of asthma were injected intratracheally with lipiodol. Roentgenograms of the chest were taken during ordinary res-

piration and during the inhalation of air under 4 to 8 cm. positive pressure. It was shown that the lumen of an isolated bronchus during positive pressure respiration did not constrict during expiration as much as it did during respiration without positive pressure. In some cases the diameter of the bronchus was 25 per cent larger with positive pressure breathing.

Based on the clinical use of positive pressure respiration, an exercise has been suggested to patients which consists in pursing the lips during expiration; this creates a positive pressure which is deflected backward into the bronchial tree. Inspiration is conducted as usual and expiration with the lips narrowed to maintain a resistance equivalent to that created by breathing outward through a tube ⅛ of an inch in diameter. This exercise pursued for two or three minutes at a time will clear up some types of continuous mild or moderate wheezing, witnessed both by subjective relief as well as the clearing of râles during expiration. In the patient with pulmonary emphysema it will also be found that the milder degrees of dyspnea are lessened by this exercise.

Livingstone [19] and others [20] have reported marked improvement from respiratory exercises. It is obvious that the ordinary breathing exercises in which the object is to inspire as deeply as possible are useless. When the asthmatic patient breathes deeply his respiration seems almost entirely upper thoracic. The lower part of the chest is already largely expanded and if it moves at all shows inward retraction. The diaphragm is thus of little or no value. The breathing exercises designed by Livingstone attempt to teach the patient to use the lower part of the chest and the diaphragm more, and to empty the lungs more completely. The patient takes a quiet inspiration followed by a long expiration, with the lips partially closed to make an F sound. Expiration is assisted by pressure with the hands on the lower part of the chest. Our own experience is limited to the simple exercise described above, namely, exhaling with the lips partially closed which in the chronic asthmatic patient and the patient with pulmonary emphysema has been found specially valuable, and which may be pursued as often as needed.

Methods of Inhalational Therapy

The recent advances in the methods of inhalational therapy have been subjected to a detailed review.[21] It should be emphasized that no one method is suitable for all patients and that the patient should generally be given the choice as to which is more comfortable for him, especially when oxygen treatment is administered at home at intervals over long periods of time. The introduction of the face tent or face mask by Argyll Campbell [22] has made possible the administration of relatively high concentrations of oxygen without more elaborate apparatus. Our own modifications of this apparatus have included recently the use of the so-called "oxyator" which works on the principle of the Bunsen burner and which sucks in a small increment of air as the oxygen passes through it. The additional flow of

this oxygen enriched atmosphere makes for increased comfort and for lower concentration of carbon dioxide in the inspired air. In the accompanying table (table 8) it will be seen that the oxygen per cent in the inspired air increased to 42 to 52 per cent as the oxygen flow is increased from 6 liters per minute to 10 liters per minute and that the CO_2 concentration is lowered from 0.9 to 0.50 per cent. This carbon dioxide concentration corresponds to that generally present in an oxygen tent as it is ordinarily administered. With higher pulmonary ventilations the per cent of carbon dioxide and of oxygen falls slightly. It is also true that haphazard employment of the face tent will not achieve as good results as are here reported. This also applies to the management of more complicated apparatus. It is our opinion, based on experimental evidence and on clinical usage, that the face tent is of considerable value in many instances [23] although it must be admitted that it rarely provides the comfort of a well ventilated oxygen tent with completely transparent pliofilm covering.

TABLE VIII

The Concentration of Oxygen and Carbon Dioxide in the Inspired Air When the Face Mask Is Used at Flows between 6 and 10 Liters per Minute

Oxygen Flow Liters/min.	20 Respirations/min.				30 Respirations/min.		
	Alveolar Oxygen per cent	Alveolar CO_2 per cent	Calculated Oxygen per cent in inspired air	CO_2 per cent in inspired air determined from gas sample during inspiration	Alveolar Oxygen per cent	Alveolar CO_2 per cent	Calculated Oxygen per cent in inspired air
6	36.3	5.7	42	0.95	34.2	5.8	40
8	41.3	5.7	47	0.85	39.8	5.7	45.5
10	46.1	5.9	52	0.50	45.4	5.6	51.0

Alveolar CO_2 Breathing air..... 5.1
Alveolar O_2 Breathing air..... 14.8

The question of expense in relation to long continued oxygen therapy merits consideration. The cost of oxygen varies at least 100 per cent depending upon the quantity of oxygen used. For patients of moderate means it is almost always possible to obtain a lower than standard rate from one of the larger companies. It is frequently desirable for the patient to purchase his own equipment, such as regulator, nasal catheter, or face tent. Depending upon the number of hours used per day the expense of oxygen treatment can then be accurately calculated and the patient or his family be informed of the possibility that in cases of pulmonary emphysema it is likely that the patient will require for the rest of his life a continuance of oxygen treatment, if his dyspnea is to be modified. Fur-

thermore, during periods of exacerbation of his illness such as might be provoked by acute respiratory infection more oxygen might become necessary.

For many patients intermittent oxygen therapy is preferable because of its simplicity, low cost and freedom from ultimate dependence on oxygen as a method of maintaining life. Periods of treatment ranging from one-half hour to one hour, two or three times in the day are of considerable help in diminishing pulmonary distention and in relieving distress. The nasal catheter with a flow of 6 liters per minute will provide an oxygen concentration of approximately 37 per cent in the inspired air; the face tent with a flow of 10 liters per minute will ensure an oxygen concentration of 50 per cent if used intelligently.

When a program of continuous oxygen therapy is decided upon, it is generally advisable to expose the patient to a gradually increasing oxygen concentration rather than suddenly to place him in an atmospheric environment which contains 50 per cent oxygen, a suggestion made to us by Palmer.[24] Patients who have suffered from chronic oxygen deficiency, especially in breathless subjects, may become irrational or stuporous when they are abruptly given a high oxygen atmosphere. The sudden change in the tension of oxygen to which the brain cells are exposed appears to interfere remarkably with their function, a circumstance which Richards and the author have noted also in the treatment of patients with chronic heart disease.[15c, d, e] The mental state may manifest itself as stupor, coma, excited delirium or depression in severe cases but it is characteristic that after a period of two to six days a rational state returns, generally with a feeling of well-being. The feeling of cheerfulness which terminates the prior upset may be paralleled by more optimistic views of his affairs outside the realm of illness.[25] This reaction, which is an interesting example of the effect of biology on psychology, does not occur except in those patients who have suffered from long-standing oxygen-want. Nevertheless, it should be borne in mind during the initiation of treatment; for patients in whom such a reaction is suspected, oxygen may be administered at a concentration of 30 per cent the first day, increasing the concentration 5 per cent each day until 50 per cent concentration is obtained. The length of time which the patient with pulmonary emphysema should be treated with 50 per cent oxygen depends on the individual patient; some of the factors involved have been mentioned previously. Whether the duration is 2 or 5 weeks, the important consideration is gradual reduction of the oxygen concentration administered. Fully two weeks should be utilized in gradually returning the patient to atmospheric air. In all of these cases, it is desirable to substitute intermittent oxygen therapy following the course of continuous treatment. In those patients who have the facilities for it, as much as 17 hours a day may be spent in an oxygen enriched atmosphere. In others, two to three half-hour periods during the 24 hours may be more feasible.

The method of administration of helium-oxygen mixtures has been described.[21] It may be mentioned here that the U. S. Government has recently released helium for medical purposes at a moderate cost. In the absence of the special apparatus designed for its use, a tent or a face mask may be employed provided flows of 25 to 30 liters per minute are maintained. The administration of helium is more apt to be successful when a trained internist, anesthetist or an expert technician is in immediate charge of the treatment. The relief of obstructive dyspnea in cases in which edematous infiltration of the bronchial walls is extensive requires time, attention and special experience.

Summary

Graphic recording of the pulmonary ventilation has been employed as a quantitative and qualitative test of respiratory function in patients with asthma and pulmonary emphysema. The effectiveness of physiologically directed therapy has been determined by this test which measures the response of the patient in terms of the total quantity of air breathed per minute as well as the velocity of air movement during the respiratory cycle.

The sensation of dyspnea in patients with asthma may be mainly attributed to an increased effort on the part of the respiratory musculature to ventilate the lungs in the presence of narrowing of the smaller bronchi. The inhalation of a helium-oxygen mixture makes possible a more normal velocity of gas movement with diminished respiratory effort. This physiological advantage in breathing helium-oxygen mixtures has been employed in the treatment of patients with severe asthma, *status asthmaticus* and asthma complicated by acute pulmonary emphysema. Of a total of 54 admissions to the hospital 28 patients showed marked improvement that could be specifically attributed to the use of helium. Twenty-one showed moderate improvement, or a combined percentage of 91 per cent. Five patients or 9 per cent showed little or no benefit from helium-oxygen therapy.

In chronic pulmonary emphysema the continuous inhalation of oxygen enriched air relieves the sensation of dyspnea in most instances. Two patients are reported in detail who suffered from severe dyspnea at rest. The oxygen saturation of the arterial blood was at or near the normal level in each case; however, an immediate and progressive fall in pulmonary ventilation resulted from the inhalation of high concentrations of oxygen, accompanied by relief of dyspnea. In one patient, a more permanent benefit took place during a period of six months intermittent oxygen treatment. This patient showed a preliminary rise in arterial CO_2 content followed by a fall during a test period of continuous residence in an oxygen enriched atmosphere. In the other patient, clinical improvement persisted only during the course of oxygen treatment over a period of two years. In the latter case only a slight decrease in arterial CO_2 content followed the previous rise. The mechanism of the rise in the carbon dioxide content of

arterial blood is discussed in 10 patients with chronic pulmonary disease treated with oxygen over relatively long periods of time. The humoral (or chemical) factor in the causation of the dyspnea of pulmonary emphysema is emphasized by the results in cases of chronic pulmonary disease treated by oxygen enriched atmospheres.

The inhalation of vaporized adrenalin in larger amounts than have hitherto been employed has been found markedly helpful in the treatment of patients with severe asthma and pulmonary emphysema. The inhalation of vaporized neo-synephrin in relatively large doses is reported as an additional helpful agent in these conditions, as a result of unpublished studies by D. W. Richards and the author. Routine use of adrenalin and neo-synephrin mixtures has been found clinically beneficial in the treatment of pulmonary emphysema. Graphic records of the pulmonary ventilation reveal, as a result of inhalation of these agents, an increased velocity of air movement, especially marked in the expiratory cycle, and an increase in vital capacity.

A simple breathing exercise consisting of pursing the lips during expiration is suggested for patients with asthma and pulmonary emphysema. The positive pressure, produced by breathing against a resistance at the lips, is reflected backward into the respiratory passageway and has the physiological advantage of reducing expiratory bronchial constriction.

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THE PRESSOR REACTION PRODUCED BY INHALATION OF CARBON DIOXIDE; STUDIES OF PATIENTS WITH NORMAL BLOOD PRESSURE AND WITH HYPERTENSION *

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THE specific stimulating action of carbon dioxide on the vasomotor centers and its pressor effect on blood pressure have been known for some time. As early as 1864, Thiry [1] observed a rise of the blood pressure of animals during the inhalation of carbon dioxide and expressed the opinion that this was the result of stimulation of the vasomotor center, which produces a constriction of the peripheral arterioles. Traube [2] later confirmed this work and also looked on carbon dioxide as an excitant of the vasomotor center. In contrast to this work, Gaskell [3] about the same time demonstrated by perfusion experiments that lactic acid dilated the arteries of the frog. Bayliss,[4] in 1901, following Gaskell's work, demonstrated by perfusion fluid through the iliac arteries that both lactic acid and carbon dioxide produced an increase in the rate of flow of blood in the skinned limb of a frog. This was interpreted as a local effect of carbon dioxide on the blood vessels. Later, in 1918, Fleisch [5] reported the results of perfusion experiments on the hind legs of frogs; he found that a low concentration (up to 3 per cent) of carbon dioxide caused arterial dilatation while stronger concentrations caused a constriction. He assumed that the dilator effect was attributable to the action on a nervous component and that the vasoconstriction was attributable to a direct action on the muscles of the arterioles.

In 1907, Henderson [6] demonstrated that carbon dioxide was necessary to maintain normal vascular tone. This he accomplished by showing that in an etherized animal or man a loss of carbon dioxide produced by overventilation of the lungs caused a marked fall in blood pressure which was relieved by the administration of carbon dioxide. From that time to 1922 numerous workers confirmed the early work on the excitant properties of carbon dioxide on various nerve centers. In 1922, Dale and Evans [7] presented evidence to show that the effect of inhalation of carbon dioxide was on the vasomotor centers in the bulb and the spinal cord. They maintained that the tonic action of the vasomotor centers was conditioned by the concentration of free carbon dioxide rather than "hydrogen ions" in the ar-

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‡ Although Dr. Brown died in November 1935, the fact that he suggested this study and supervised it in its early stages seemed to the surviving authors to require that the paper be indexed under his name.

terial blood. This may be attributable to the great power of carbon dioxide to penetrate all membranes.

Porter [8] during the war used a 3 per cent concentration of carbon dioxide to increase the blood pressure of soldiers who were in a state of shock. In 1922, Schneider and Truesdell [9] demonstrated that inhalation of 1 to 8 per cent carbon dioxide by normal individuals was followed by an increase in the pulse rate, an increase in the systolic and diastolic blood pressure and an increase in the pulse pressure, particularly after the concentration of carbon dioxide had reached 3 per cent.

Raab,[10, 11] in 1929, reported that during the inhalation of carbon dioxide the increase in the blood pressure of patients who had essential hypertension was several times as great as that noted in a group of normal persons. He attributed these increases in blood pressure to an increased sensitivity of the vasomotor centers to changes in carbon dioxide tension. Many investigators have been concerned with the question as to whether essential hypertension is central or peripheral in origin. Ellis and Weiss,[12] in 1930, showed that the increased blood pressure in cases of hypertension is the result of a contraction of the peripheral vascular system and that it is not the result of primary changes in the general blood volume, cardiac output, circulation through the lungs, or velocity of the blood flow. Investigators have assumed that diminishing the supply of blood and oxygen to vasomotor centers was the most essential condition for increased activity of these centers. Another assumption is that the accumulation of acid substances, particularly lactic acid, which results from a lack of oxygen, is a factor in increasing activity or tonus of the vasomotor centers. This forms the basis of the most recent hypothesis of essential hypertension. In 1931, Raab [13, 14] attempted to produce essential hypertension in animals in an effort to determine its pathogenesis. He produced hypertension by irritation of the vasomotor centers by decreasing the supply of oxygen or by a perfusion of the hypothetical vasomotor centers with lactic acid. When inhalation of carbon dioxide was added to either or both of these conditions a considerably greater rise in blood pressure occurred. This increased sensitivity also could be produced by purely nervous stimuli from the periphery. Raab concluded that essential hypertension could be considered the result of local deficiency of oxygen and the accumulation of lactic acid within the vasomotor centers of the brain stem as a consequence of disturbances in the local circulation, such as spasm or sclerosis. The actual blood pressure in hypertension would accordingly be determined by the sum of the stimuli resulting from oxygen deficiency and accumulation of lactic acid and also by the abnormally increased responses of blood pressure to the stimulus of the normal carbon dioxide tension of the blood and different kinds of sensory and emotional stimuli.

The more recent conception of the fundamental abnormality in cases of essential hypertension is that the central vasomotor mechanism is hypersensitive and reacts excessively to many forms of stimulation, such as

those which are sensory, thermal, and emotional. Changes in circulation of the brain which result from organic arterial disease or spasm do not appear to play a rôle in elevation of blood pressure in cases of hypertension except in the later stages. Studies which have been made on the constitutional nature of essential hypertension by employing a standard stimulus [15, 16] (cold), which effects a sharp, thermosensory vasopressor reflex, are important. The hyperreactive vasopressor response to cold is present during the early life of most children of hypertensive parents. It would be difficult to assume that organic or circulatory factors exist in the brain of persons who eventually will have hypertension.

The present study was carried out to determine whether the pressor reactions of normal and hypertensive persons were qualitatively or quantitatively different following the inhalation of carbon dioxide, and to compare these responses with those which occur as a result of the cold test.

Material

The tests were carried out on 65 patients; 24 of these patients had a normal blood pressure and 41 had varying degrees of hypertension. All were ambulatory patients and none had evidence of cardiac or renal insufficiency. The ages of the patients varied from 20 to 60 years; 36 were men and 29 were women. For the observations the patients were divided into two groups depending on the method of study employed.

Group 1 was composed of 45 patients. This group was further subdivided into three groups: Group A was composed of 15 patients whose blood pressure was normal. Group B was composed of 21 patients who had essential hypertension without demonstrable organic change in the arterioles of the retinae except as shown in the table which deals with this group. Group C was composed of nine patients who had essential hypertension which was associated with definite organic changes in the arteries of the retinae.

Group 2 consisted of 20 patients; 9 had a normal blood pressure and 11 had varying degrees of hypertension. The distribution according to age and sex was similar to that in group 1.

Methods

Cold Test. In performing the cold test the patient is placed in a recumbent position for 30 minutes, or until the blood pressure has attained the basal level. The cuff is placed on one arm of the patient and the hand on the opposite side is placed in ice water at 4° C. well above the wrist for one minute. The value for the blood pressure is determined at least three times while the hand is in the ice water. The highest value for the systolic and diastolic pressure is recorded as the measure of response. The hand is then removed from the ice water.

Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen. Before the inhalation of carbon dioxide the patient is placed in a recumbent

position for 20 minutes until the basal blood pressure and basal pulse rate are established. The mask which is used to insure proper inspiration of the carbon dioxide is put on the patient and allowed to remain until he becomes accustomed to breathing with it on and until the blood pressure and pulse rate return to approximately basal levels. The mask is then attached to a tank which contains a mixture of 10 per cent carbon dioxide and 90 per cent oxygen; this mixture is administered for five minutes. The blood pressure and pulse rate are recorded every minute. The number of respirations are noted. No ill effects were noted from the inhalation of the carbon dioxide; whatever minor distress (slight dyspnea, light headedness, and so forth) was present quickly disappeared when the inhalation of carbon dioxide was discontinued. The number of respirations was slightly increased (an average of eight) while the depth was definitely increased. The pulse rate increased while the patients breathed carbon dioxide. This is discussed more fully in the consideration of the various groups.

The difference between the studies in group 1 and group 2 was that in group 1, in addition to the preliminary cold test another similar test was performed during the inhalation of carbon dioxide. In group 2 the second cold test was performed five minutes after the removal of the mask, when the blood pressure had returned to the previous basal levels.

Data Obtained from Study of Patients in Group 1

Cold Test. The results obtained in group A are shown in tables 1 and 2. The average increase in blood pressure from the basal level in this group during the application of the cold test was 13.4 mm. of mercury for the systolic pressure and 11 mm. for the diastolic pressure. In group B (tables 2 and 3) the average increase in blood pressure from the basal level was 28.9 mm. of mercury for the systolic pressure and 19.1 mm. for the diastolic pressure. In group C the average increase in blood pressure from the basal level was 32.4 mm. of mercury for the systolic pressure and 24.5 mm. for the diastolic pressure.

The Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen. In group A the inhalation of 10 per cent carbon dioxide caused an average increase in the blood pressure from the average basal level, of 25.2 mm. of mercury for the systolic pressure and 14.6 mm. for the diastolic pressure (tables 1 and 2). In four cases in which the blood pressure was normal, no increase occurred or the increase was less than that produced by the cold test alone. The pulse rate increased an average of eleven beats for each minute that the carbon dioxide and oxygen were inhaled. In six cases the increase was negligible, while in the three cases in which there was the greatest increase in systolic blood pressure during the inhalation of carbon dioxide and oxygen, the increase in the pulse rate was the greatest (20 to 40 beats per minute). In Group B the inhalation of carbon dioxide and oxygen caused an average increase of 33.7 mm. of mercury in the systolic

TABLE I

Effects of Cold and Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen on the Blood Pressure in Group A

Case	Age, years, and sex	Systolic and diastolic blood pressure, mm. of mercury			
		Basal values	During application of cold	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen and application of cold
1	42 M	115/73	128/75	120/90	138/100
2	24 F	114/80	122/94	136/103	140/110
3	48 F	120/75	128/85	120/80	140/90
4	35 M	110/80	120/85	120/90	140/100
5	36 M	112/75	120/85	130/80	130/80
6	20 M	110/75	125/85	130/80	130/90
7	43 M	118/74	128/86	150/85	160/90
8	28 M	110/80	125/80	160/100	160/100
9	27 M	110/70	120/80	160/100	160/100
10	27 F	110/78	130/90	130/80	130/82
11	29 F	86/60	104/80	130/80	130/80
12	37 M	88/68	98/70	105/70	110/70
13	29 F	90/65	115/90	124/94	130/95
14	49 M	75/50	87/68	110/80	110/75
15	26 M	108/65	128/80	130/75	140/85
Mean values	Systolic pressure	105.1±2.3	118.5±2.3	130.3±2.8	136.5±2.7
	Diastolic pressure	71.2±1.5	82.2±1.3	85.8±1.7	89.8±1.9

TABLE II

Effects of Cold, Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen, and the Application of Cold during the Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen in Group 1

Group	Cases	Systolic and diastolic blood pressure, mm. of mercury			
		Average basal values	Average increase during:		
			Cold test	Inhalation of 10 per cent carbon dioxide and 90 per cent oxygen	Inhalation of 10 per cent carbon dioxide and 90 per cent oxygen and application of cold
A (blood pressure normal)	15	105.1/71.2	13.4/11.0	25.2/14.6	31.4/18.6
B (hypertension without organic changes in retinal arteries)	21	134.3/87.8	28.9/19.1	33.7/20.1	48.5/28.1
C (hypertension with changes in retinal arteries)	9	156.3/105.1	32.4/24.5	23.4/15.7	35.7/25.8
B and C (hypertension)	30	140.9/93.0	30.0/20.7	30.6/18.8	44.6/27.4

pressure and 20.1 mm. in the diastolic pressure. In 11 cases no increase in blood pressure occurred or the increase was less than that produced by

TABLE III

Effects of Cold and Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen on the Blood Pressure in Group B

Case	Age, years, and sex	Changes in ocular fundi	Systolic and diastolic blood pressure, mm. of mercury			
			Basal values	During application of cold	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen and application of cold
1	34 M	0	140/98	150/100	150/100	155/105
2	42 F	0	140/100	162/108	130/90	154/100
3	25 M	0	130/86	152/100	152/92	165/110
4	47 F	0	120/76	160/100	155/100	175/110
5	23 M	0	132/90	154/110	165/115	172/117
6	47 M	0	140/108	180/140	158/120	180/140
7	45 M	Arterioles narrowed	125/100	145/115	125/100	155/110
8	49 M	Arterioles narrowed	120/80	140/100	160/110	160/112
9	22 M	Arterioles narrowed	140/78	158/105	165/100	175/100
10	43 F	Arterioles narrowed	135/95	165/120	180/120	200/130
11	27 M	Arterioles narrowed	152/82	180/100	190/118	210/120
12	49 F	Arterioles narrowed	150/80	170/90	195/110	210/115
13	41 F	Arterioles narrowed	150/100	180/120	210/130	210/130
14	43 M	Arterioles narrowed	150/90	230/148	220/120	240/160
15	38 M	Arterioles narrowed	150/98	190/110	190/115	205/120
16	60 M	Arterioles narrowed	130/58	164/80	190/100	200/100
17	26 F	Arterioles narrowed	132/100	165/100	200/130	208/140
18	36 M	Arterioles narrowed	140/80	152/100	170/100	190/110
19	26 F	Arterioles narrowed	105/70	150/109	145/95	162/100
20	21 M	Arterioles narrowed	130/90	142/90	140/108	152/105
21	31 M	Arterioles narrowed	110/85	140/100	138/92	160/100
Mean values	Systolic pressure		134.3±2.0	163.2±3.2	168.0±4.0	182.8±3.7
	Diastolic pressure		87.8±1.8	106.9±2.3	107.9±1.7	115.9±2.4

the cold test alone. In group B the average increase in pulse rate during the inhalation of carbon dioxide and oxygen was 17 beats per minute. There was no apparent correlation between the increase in pulse rate and the in-

crease in blood pressure. In group C (tables 2 and 4) the average increase in the blood pressure during the inhalation of carbon dioxide and oxygen was 23.4 mm. of mercury for the systolic pressure and 15.7 mm. for the diastolic pressure. This was less than the average increase produced by the cold test alone for this group. The average increase in pulse rate was 11 beats per minute.

The Application of the Cold Test during the Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen. In group A (tables 1 and 2),

TABLE IV

Effects of Cold and Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen on the Blood Pressure in Group C

Case	Age, years, and sex	Changes in ocular fundi	Systolic and diastolic blood pressure, mm. of mercury			
			Basal values	During application of cold	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen and application of cold
1	43 F	Sclerosis, grade 1	120/80	150/110	152/106	156/120
2	33 F	Sclerosis, grade 1	140/95	158/110	154/112	172/120
3	40 F	Sclerosis, grade 1	152/110	180/130	175/120	200/150
4	32 F	Sclerosis, grade 1	135/100	170/120	170/125	180/130
5	33 F	Sclerosis, grade 1	180/130	235/160	190/140	180/130
6	48 F	Sclerosis, grade 1	140/96	180/112	182/120	200/125
7	57 M	Sclerosis, grade 3, and hemorrhages	190/125	220/175	210/135	230/155
8	51 M	Sclerosis, grade 3	140/100	150/110	140/100	150/110
9	44 F	Arterioles narrowed	210/110	255/140	245/130	260/138
Mean values		Systolic pressure	156.3±6.8	188.7±8.63	179.7±7.4	192.0±7.9
		Diastolic pressure	105.1±3.5	129.6±5.5	120.8±3.2	130.9±3.3

when a cold test was performed during the inhalation of 10 per cent carbon dioxide and 90 per cent oxygen, the average increase was 31.4 mm. of mercury for the systolic pressure and 18.6 mm. for the diastolic pressure. These increases were greater than those which were produced by either the cold test alone or the inhalation of carbon dioxide and oxygen. However, in seven cases in this group the increase in blood pressure produced by the application of the cold test during the inhalation of carbon dioxide and oxygen was no greater than the increase produced by the inhalation

of carbon dioxide. In group B (tables 2 and 3) the application of cold during the inhalation of carbon dioxide and oxygen produced an average increase of 48.5 mm. of mercury in the systolic pressure and an average increase of 28.1 mm. in the diastolic pressure. These were the greatest increases noted in group 1. The increase in the systolic pressure was three and six-tenths greater and the increase in the diastolic pressure was two and a half times greater than were the increases which occurred in the systolic and diastolic pressures respectively when normal persons were subjected to the cold test. The increase in the systolic and diastolic pressure was one and nine-tenths greater than that which was obtained when normal persons were inhaling carbon dioxide and oxygen. The increase in the systolic pressure was one and six-tenths greater and the increase in the diastolic pressure was two and four-tenths greater than were the increases which were obtained in these respective pressures when the cold test was applied to normal persons who were inhaling carbon dioxide and oxygen. In group C (tables 2 and 4) the application of cold during the inhalation of carbon dioxide and oxygen produced an average increase of 35.7 mm. of mercury in the systolic pressure and an average increase of 25.8 mm. in the diastolic pressure. These increases were not as great as the respective increases which were obtained in the group of patients who had pre-organic hypertension (group B), but in group C the average value for the systolic pressure was 22 mm. of mercury higher and that for the diastolic pressure was 17.3 mm. higher than were the respective values in group B. In all but one of the cases in group C the increases in the systolic and diastolic blood pressure which were produced when the cold test was applied during the inhalation of carbon dioxide and oxygen were greater than the increases which were produced by the inhalation of carbon dioxide and oxygen.

When the patients who had hypertension (groups B and C) were considered as a single group it was found that the increases in blood pressure which were produced by the application of cold, by the inhalation of carbon dioxide and oxygen and by the application of cold during the inhalation of carbon dioxide and oxygen were nearly twice as great as were the increases which were produced in cases in which the blood pressure was normal (group A). However, this same quantitative difference was produced by the cold test alone at a lower level of blood pressure.

Data Obtained from Study of Patients in Group 2

Group 2 included 9 persons whose blood pressure was normal and 20 patients who had varying degrees of hypertension. In the study of this group the cold test was not performed during the inhalation of carbon dioxide and oxygen but was performed five minutes after the inhalation had been discontinued and the blood pressure had returned to the previous basal levels. This was done in order to determine whether the vasomotor centers would be more sensitive to the application of cold following the inhalation of carbon dioxide and oxygen than they were before or during the inhala-

tion. In the nine cases in which the blood pressure was normal the application of cold produced an average increase of 15 mm. of mercury in the systolic pressure and an average increase of 13 mm. in the diastolic pressure. During the inhalation of 10 per cent carbon dioxide and 90 per cent oxygen, the average increase in the systolic pressure was 39 mm. of mercury and the average increase in the diastolic pressure was 21.8 mm. The application of cold five minutes after the inhalation of carbon dioxide and oxygen had been discontinued produced an average increase of 17.7 mm. of mercury in the systolic pressure and an average increase of 16.6 mm. in the diastolic pressure. These increases were similar to those which were produced by the application of cold before the inhalation of carbon dioxide and oxygen. The average increase in the pulse rate during the inhalation of carbon dioxide and oxygen was 20 beats per minute. This was slightly greater than the increase noted in group 1.

In the eleven cases in which the patients had varying degrees of hypertension the application of cold produced an average increase of 37.4 mm. of mercury in the systolic pressure and an average increase of 25.7 mm. in the diastolic pressure. The inhalation of carbon dioxide and oxygen produced an average increase of 54.8 mm. of mercury in the systolic pressure and an average increase of 32.4 mm. in the diastolic pressure. Five minutes after the inhalation of carbon dioxide and oxygen had been discontinued the application of cold produced an average increase of 30.3 mm. of mercury in the systolic pressure and an average increase of 28.8 mm. in the diastolic pressure. In a very few cases the increases which were observed when cold was applied five minutes after the inhalation of carbon dioxide and oxygen had been discontinued were slightly greater than the increases which were observed when cold was applied before the inhalation. In cases in which cold was applied one or two minutes after the inhalation of carbon dioxide and oxygen had been discontinued the increases were greater than those observed when cold was applied before the inhalation, but this response disappeared five minutes after the inhalation had been discontinued. The effect of carbon dioxide on the vasomotor center apparently disappears in about five minutes.

Comment

The inhalation of 10 per cent carbon dioxide and 90 per cent oxygen produced an increase in the blood pressure of normal and hypertensive persons. There was no qualitative difference in the vasopressor response of normal and hypertensive persons but a significant quantitative pressor reaction was obtained when cold was applied during the inhalation of the carbon dioxide and oxygen. When groups B and C were considered as a single group we found that the average increases produced in the blood pressure by the application of cold were the same as those produced by the inhalation of carbon dioxide and oxygen. When the cases of hypertension were divided into those in which the hypertension was in the early or pre-organic stage and those in which the hypertension was in the advanced stage it was found

that the increases which were produced in the blood pressure by the application of cold were greater in cases of early or pre-organic hypertension than they were in cases of advanced hypertension. This was particularly true when cold was applied during the inhalation of carbon dioxide and oxygen. The basal blood pressure was lower in cases of pre-organic hypertension than it was in cases of advanced hypertension. If the actual height or "ceiling" of the blood pressure is used as a criterion, the blood pressure was higher in cases of advanced hypertension. The average increases in the blood pressures of normal and hypertensive persons were greater when cold was applied during the inhalation of carbon dioxide and oxygen than they were when cold was not applied during the inhalation. This confirms the experimental work of Raab. This effect may be said to be the result of the combined action of several stimuli. The recent work of Bolton, Carmichael and Williams [17] did not reveal that alteration in the tension of gas in the blood affected the peripheral vessels. The vascular responses produced by the inhalation of carbon dioxide and oxygen are dependent on the integrity of the sympathetic nervous system and are under the control of the central nervous system. Since carbon dioxide has a specific stimulating effect on the vasomotor centers, the definite increase in blood pressure which occurs during the inhalation of carbon dioxide and oxygen may be assumed to indicate some hypersensitivity of the vasomotor centers. When cold was applied during the inhalation of carbon dioxide and oxygen a further increase took place. This might have been caused by a reflex transmission of peripheral stimulation to a higher reactive central mechanism that was still further sensitized by the increased concentration of carbon dioxide in the blood, but the response was most likely the result of several stimuli.

These observations are important in attempting to explain the disturbed mechanism in essential hypertension. They demonstrate that a stimulus applied to the periphery (local application of cold), or applied centrally by increasing the carbon dioxide concentration in the blood, increased the blood pressure of normal and hypertensive persons. They throw no light on the question as to why the hypertensive person responds to a greater extent than does the normal person. Whatever the fundamental fault is, it does not occur in adult life with the onset of high blood pressure, but occurs years before there is an increase in the blood pressure. This fault concerns the constitutional nature of the behavior of the autonomic nervous centers and may be influenced by hereditary factors. Similar physiologic faults will probably be found in other centers which regulate autonomic nervous activity. It is futile to make hypotheses in the present state of our knowledge. The entire question of differences in psychic behavior, in personality, and in the reaction of the central nervous system to its environment is intimately concerned in this problem.

Summary

The results which we obtained with the cold test alone were comparable to those obtained by Hines and Brown on normal and hypertensive persons.

The inhalation of 10 per cent carbon dioxide and 90 per cent oxygen produced an increase in the blood pressure of both normal and hypertensive persons. The increase in blood pressure was greater and the ultimate height reached was greater in cases of hypertension than it was in cases in which the blood pressure was normal. The studies did not produce any evidence as to why the hypertensive person responds to a greater degree than does a normal person.

The increase in blood pressure produced by the application of cold during inhalation of carbon dioxide and oxygen might be interpreted as the result of a reflex transmission of peripheral stimulation to a higher reactive central mechanism that was still further sensitized by the increased concentration of carbon dioxide in the blood, but the response most likely is the combined result of several stimuli.

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CONSTITUTIONAL REACTIONS FROM BACTERIAL VACCINES *

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ALTHOUGH much has been written about local and focal reactions, little or no attention has been paid to constitutional reactions from bacterial vaccine injections. These systemic bacterial reactions are entirely different from the constitutional reactions sometimes encountered following treatments with food, animal epidermal, pollen, or other kinds of protein extracts. An overdose of vaccine will frequently cause an aggravation of the patient's trouble, but the type of constitutional reaction that I am about to describe is a definite shock reaction, comparable to that produced by the intentional intravenous injection of a small dose of typhoid vaccine in foreign protein therapy.

In allergic individuals, constitutional reactions from food, animal epidermal, pollen, or other nonbacterial protein extracts, almost always occur inside of 30 minutes following the injection, and manifest themselves as itching of the palms of the hands, or irritation of the nose and throat, or as a definite attack of urticaria, hay-fever, or asthma. Whenever any of the dose is accidentally injected into a blood vessel, the constitutional reaction takes place almost instantaneously.

The bacterial type of constitutional reaction manifests itself within one-half hour to several hours following the vaccine injection. It always starts with a chill, which may vary from mere chilly sensations to a definite, shaking chill. Nausea and vomiting occasionally occur at this stage, particularly in children. The chill is soon succeeded by fever ranging anywhere from 100° to 105°. There is malaise, and usually aches and pains throughout the body. The reaction simulates quite closely, therefore, the early stages of an attack of grippe or influenza. After a few hours, however, the temperature usually returns to normal, and by the next day the patient has either fully recovered, or is left with only a feeling of weakness which soon passes off. Occasionally, the fever persists until the following day. Although such a reaction is not necessarily dangerous, it is decidedly unpleasant, and may cause a nervous patient to become apprehensive about subsequent vaccine treatment.

This type of constitutional reaction which occasionally occurs in bacterial vaccine therapy, is never encountered in treatment with food, animal epidermal, pollen, or other kinds of protein extracts. It can happen with both stock and autogenous vaccines, and in nonallergic as well as allergic individuals. Although a constitutional reaction is more likely to occur following the larger doses of a strong vaccine, it is not dependent upon the size of the dose for its production, as it can follow a repeated dose of the

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same vaccine, where the preceding dose had failed to produce any unpleasant symptoms.

This distinctive type of constitutional reaction is evidently due to accidental injection of some or all of the vaccine dose into a blood vessel, as the symptoms can be duplicated by an intentional intravenous injection of bacterial vaccine. A subcutaneous injection of a dose of potent vaccine is almost always followed by a local reaction which can be both seen and felt, reaching its height in about 24 hours. When a vaccine treatment is followed by a constitutional reaction, however, there is almost invariably a negligible local reaction, or even none at all, indicating that some or all of the dose has been abruptly carried away from the site of injection.

The way to prevent these bacterial protein shock reactions is to keep the vaccine from directly entering the blood stream, by means of the following precautions. Because of its lack of vascularity, the outer part of the upper arm, about midway between shoulder and elbow, is the best site for vaccine injections. After the hypodermic needle has been inserted subcutaneously, but before any of the vaccine is injected, the piston of the syringe should be sharply retracted to see if any blood comes back into the syringe. If blood appears, the needle should be withdrawn and inserted in another spot, and the piston retraction repeated, before the dose of vaccine is actually injected. The vaccine should be injected slowly, and with the larger doses, the syringe piston should be retracted several times during the course of the injection to make sure that the tip of the needle has not slipped into a small blood vessel. After all of the dose is injected, a small pledget of sterile cotton, moistened with alcohol, should be pressed over the site of injection and held there while the needle is being withdrawn and for a short time thereafter, to prevent any of the vaccine from tracking back through the needle wound into a superficial vessel that may have been punctured by the passage of the needle through the tissues. I consider this last precaution to be quite important in the prevention of constitutional reactions. The injection site should never be massaged. By careful observance of the above-mentioned technic it is possible, except on rare occasions, to prevent the vaccine from immediately entering the blood stream.

Treatment of these shock reactions when they do occur, consists of the oral administration of ephedrine and amytal (iso-amyl ethyl barbituric acid), or ephedrine with phenobarbital, and rest in bed during the brief febrile stage.

SKIN TESTING FOR BRUCELLOSIS (UNDULANT FEVER) IN SCHOOL CHILDREN *

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In human beings cutaneous hypersensitivity to organisms of the genus *Brucella* was first investigated by Fleischner and Meyer [1] in 1918. Using a saline suspension of organisms they tested 75 infants who had been fed milk containing *B. abortus* and found two with a specific skin sensitivity. Burnet,[2] subsequently, used a broth filtrate and demonstrated a relationship between skin reactivity and the presence of specific agglutinins in the blood stream. Since then the test has been used frequently for the diagnosis of undulant fever [3, 4, 5, 6, 7, 8, 9, 10, 11] also in surveys designed to evaluate the incidence of infection in various occupational groups, such as meat packers, veterinarians and laboratory workers.[12, 13, 14, 15, 16] The variety of antigens which have been used precludes specific comparison of the results of investigators, though they have usually agreed that a positive skin test indicates some past contact with the organism. The high percentage of positive reactors in those groups closely associated with animal carcasses and persons with long periods of association with domestic animals points strongly to animal contact as an important factor in the development of the positive reaction.

Certain observations have made the interpretation of the skin test difficult. For instance, some individuals from whose blood *B. abortus* has been cultivated have been shown to have negative skin reactions.[19, 20, 21, 22, 23, 24] Moreover, it is common experience that many individuals develop hypersensitivity to the antigen without having been aware of symptoms or signs of the disease. Furthermore, for years after recovery from the disease skin reactivity is usually retained. Therefore, the skin test may seem of little value in the diagnosis of the individual case, but further knowledge of the epidemiology and incidence of brucellosis in man may be gained by its use on large groups. The following report presents data secured on children of school age in Kansas City, Kansas, in the course of one of three surveys conducted by the National Institute of Health to study the incidence of chronic brucellosis.

Kansas City, Kansas, has an urban population of 126,000 divided into five districts which grew up independently and are separated by such boundaries as ravines, rivers and transportation systems. The incidence of Bang's disease among dairy herds supplying milk to this community as

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We wish to express our appreciation for the hearty coöperation of the Kansas State Board of Health, Dr. Clifton Hall, and Dr. Alice Evans of the National Institute of Health.

determined by agglutination tests performed during the last ten years has varied from 12 to 27 per cent. Rapid method agglutination tests which have been made in local private and hospital laboratories during the past two years revealed that 5 per cent of 5000 sera tested were positive in dilutions of 1:10 or higher.

Not only the factor of milk consumption but that of age should be considered in a group of school children. It has long been assumed that the greater percentage of positive skin reactors to various bacterial antigens in older age groups was explicable on the basis of prolonged exposure and subclinical infections. That these are the sole factors involved has been questioned, several investigators having suggested that age *per se* may be a factor in determining skin reactivity. Various investigations which have supported this view have been reviewed by Baumgartner.[17] It is now accepted that the skin of the very young infant does not react like that of the older subjects regardless of the immune state involved. This difference may be of no importance in the present study, but it does seem of some interest to point out that infections due to brucellae in children have been infrequently reported in the literature although the greater exposure through milk ingestion would obviously be in younger age groups.

Methods

The antigen used for intradermal tests was Huddleson's[18] "brucellergin," a fat-free nucleoprotein derivative, kindly supplied by him. For the tests 0.1 c.c. of a 1:10,000 dilution was used. Readings were made in 48 hours. Tests were considered positive only if erythema and edema measuring at least 5 by 5 mm. were present.

The school children were given routine tuberculin tests * (0.0005 mg. P.P.D.) on the opposite arm at the same time the brucellergin skin tests were performed.

In the control experiments, comparing the results of tests made with brucellergin and heat-killed vaccine, 0.04 c.c. of the latter was used for each test, both tests being made simultaneously, one on each forearm. Readings were made after 48 hours and after 7 days. The vaccine used was standardized to a nephelometer number 3 which represents approximately 6 billion organisms per c.c.

Results

1. *Comparison of Brucellergin and Heat-Killed Vaccine in Skin Tests.* One group of 168 persons was tested simultaneously with both vaccine and brucellergin. The results are summarized in table 1. The subjects were all inmates of a county farm, public charges, some of whom had been moved from other institutions, many of whom had lived for years under some kind of institutional regime. Positive reactors had been found in the

* These tuberculin tests were performed by Dr. Clifton Hall of the Kansas State Department of Health.

herds supplying one of the institutions, in which these subjects had been housed—though satisfactory data concerning the incidence of herd infections were lacking. Readings were recorded as follows:

— no reaction or one measuring less than 5 by 5 mm. at 48 hours and no reaction in 8 days.
+ reaction measuring 5 by 5 mm. or over but less than 10 by 10 mm. at 48 hours and little or no reaction at 8 days.
++ reaction of 10 by 20 mm. at 48 hours, persistent reaction at 8 days with slight pigmentation.
+++ more than 20 by 20 mm. erythema and edema at 48 hours with persistent reaction at 8 days.
++++ more than 30 by 30 mm. reaction at 48 hours and ulceration at 8 days.

TABLE I

Comparison of Results in Intradermal Tests with Brucellergin and Vaccine in 163 Persons

Type of Antigen	Number of Persons Exhibiting Reactions					
	−	+	++	+++	++++	Total
Brucellergin	119	21	12	11	0	163
Vaccine	74	42	27	11	9	163

The severity of the reactions with the two antigens differed, though in the same person the same relative degree of severity was found, i.e., the person with a ++++ reaction to vaccine had a +++ reaction to brucellergin, the most severe reaction found with this antigen. The ++++ reactions were those with ulceration and found only when vaccine was used. Brucellergin detected these very sensitive individuals but gave rise to less severe reactions.

Blood was taken from 14 of the more severe reactors seven days after skin testing and the sera tested for specific agglutinins and opsonocytophagic activity, using the technics described by Evans.[25] In all but one individual specific agglutinins were demonstrated in dilutions varying from 1:10 to 1:320. Two months later 13 of these subjects were retested. All gave positive agglutinin reactions, 11 of the 13 with higher titers—two as high as 1:1280. This sharp rise in agglutinin titer was attributed to the antigenic properties of the material used for skin tests, because the subjects showed little evidence of concomitant disease. They were, however, old people with many complaints and reliable histories and clinical studies were not available. The marked increase in the agglutinin titer (1:10 to 1:1280 for example) from seven days to two months after the initial skin test indicates that the results of agglutination tests should be regarded with suspicion if the individual has previously been skin tested. Opsonocytophagic

activity varied so much in the two months interval between testings that no significant statement concerning the influence of skin testing on this phenomenon can be made.

2. *The Relationship of Skin Sensitivity to Age.* Table 2 summarizes the results of brucellergin skin tests on 7,122 school children.

TABLE II

Relationship of Age to the Result of Intradermal Brucellergin Tests in 7,122 Children

Age	Male		Female		Total		
	Tested	Positive	Tested	Positive	Tested	Positive	Per cent Positive
4–9	629	32	584	37	1213	69	5.7
10–14	1671	172	1729	160	3400	332	9.7
15–19	1353	152	1156	89	2509	241	9.6
Total	3653	356	3469	286	7122	642	9.0

Nine per cent of the entire group gave positive reactions. The children less than 10 years of age showed a significantly lower percentage of positive reactions (5.7). In the two older age groups (10–14 and 15–19) about the same percentages of positive reactions were found (9.6). The only difference between the sexes was found in the 15–19 year group of white children, with 11.2 per cent of males and 7.7 per cent of females showing positive skin tests. This difference was not found in colored children of this age.

3. *Analysis of Results by Schools.* In table 3 a comparison of the results in the different schools shows a range in percentage of positive reactors from 2.7 to 18.1.

TABLE III

Comparison by Schools

	Number Tested	Number Positive	Per cent Positive
Junior and Senior High A	711	129	18.1
Junior and Senior High B	1181	146	12.36
Junior and Senior High C	1135	107	9.42
Junior and Senior High D (Colored)	1117	31	2.7
Grade Schools A	2776	203	7.3
Unclassified	202	26	12.8

The highest percentage was found in the junior and senior high schools located in the southwestern section of the city. Here, the population is relatively less dense and many families keep milk cows, goats, hogs and chickens. Many of these people drink raw milk not controlled by city regulations and also they may have direct contact with infected animals.

A survey showed that at least two-thirds of all families keeping animals in the city live in this section. On the other hand, in the northeastern section of the city where the population is almost entirely colored and virtually no domestic animals are kept, only 2.7 per cent of students in the junior and senior high schools showed positive skin reactions. The milk consumed in this area is bought from dairies or grocery stores where the supply is regulated by the city milk ordinance.

4. *Results in White and Colored Children.* A summary of the data on white and colored children is given in table 4.

TABLE IV

Comparison of Skin Sensitivity in White and Colored Students

Color	Persons Tested	Positive Reactors	
		Number	Percentage
White	6005	611	10.1
Colored	1117	31	2.7
Total	7122	642	9.0

Two and seven-tenths per cent of 1117 colored children were sensitive to brucellergin and 10.1 per cent of 6005 white children. The colored students tested were all in junior and senior high schools. The difference between the two races is, therefore, more marked than these figures indicate because 1213 of the 6005 white students tested were under 10 years of age, the age group with a lower percentag of positive reactors.

5: *The Possible Relation to Milk Supply.* The marked difference found in the numbers of positive reactors in the colored and white populations may be due to differences in their dietary habits. Ninety-eight and eight-tenths per cent of the raw milk sold in the city is used by the whites and 1.2 per cent by the colored population, although the latter constitutes 16.31 per cent of the total population. The daily per capita consumption of milk (exclusive of cream and buttermilk, both of which were negligible) averaged 0.211 pints in the colored group as compared with 0.521 pints consumed by the whites. Furthermore, 92.9 per cent of the milk consumed in the colored areas was pasteurized, and canned milk was a very popular item of the diet. Only 49.4 per cent of the milk consumed by the white population was pasteurized. The milk supply was verified in families in which there were children with positive reactions. This was possible in 614 of the 642 positive reactors. The results are tabulated in table 5.

Four hundred and eighty-seven, or 79.3 per cent of the persons with positive skin tests used raw milk. Since milk is commonly bought in grocery stores and the source of supply may change without the knowledge of the consumer it is difficult to state with certainty that a given family

TABLE V

The Type of Milk Consumed by 614 Persons with Positive Skin Tests

Milk Used	Number Cases	Percentage
Raw	487	79.3
Pasteurized	125	20.3
Canned	2	0.4
Total	614	100.0

used raw or pasteurized milk exclusively. The data are also complicated by the fact already mentioned that some of these children were directly exposed to animals. However, it appears that there is some relationship between the milk supply and percentages of positive reactors.

6. *The Relationship of the Results of Brucellergin and Tuberculin Tests.* The relationship of brucellosis and tuberculosis, both occurring in chronic and latent forms, and both related epidemiologically to bovine sources, presents interesting similarities. Here it is pertinent to present briefly only the results of the two specific skin tests, simultaneously performed.

TABLE VI

Relationship of Hypersensitivity to Tuberculin and Brucellergin in 7,122 Children

Result of Test		Number of Persons
Tuberculin	Brucellergin	
+	+	132
−	+	510
+	−	1864*
−	−	4616

* Personal communication from Dr. Clifton Hall of the Kansas State Department of Health.

The results indicate that there is no correlation between positive brucellergin and positive tuberculin reactions. In colored schools in which the percentages of brucellergin reactions were the lowest, the percentages of positive tuberculin reactions were among the highest found (45.0 and 62.8 per cent). In other schools though the differences were not so striking, the same lack of correlation was apparent.

7. *The Clinical Picture in the Sensitive Subject.* An analysis has been made of the clinical symptoms in the positive reactors.[26] The results of this study confirmed our belief that many of these children had chronic complaints which were probably due to the ambulatory type of brucellosis.

SUMMARY

Simultaneous intradermal tests on adults with vaccine and brucellergin indicated that heat-killed vaccine produces more severe reactions than brucellergin. In all of the 13 cases investigated skin testing was followed by a rise in titer of specific agglutinins.

Intradermal tests with brucellergin in 7122 school children gave the following results:

1. Positive reactions were found in 9.0 per cent.
2. There was an increasing percentage of positive skin reactors in successive age groups up to early adulthood.
3. Differences in reactions of males and females were found only in the 15–19 year old group and then only in white children.
4. The lowest percentage of positive reactions was found in the colored children.
5. Seventy-nine and three-tenths per cent of the positive reactors consumed raw milk.
6. There was no correlation between positive brucellergin and positive tuberculin reactions.

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SYPHILIS AND GONORRHEA AS PUBLIC HEALTH PROBLEMS *

By JOHN L. RICE, M.D., Commissioner of Health, *New York, N. Y.*

THE basic principles of a syphilis and gonorrhea control program are essentially the same for all communities. Differences may exist in the manner of administration and in the volume of service performed, but the problem of controlling these diseases and its solution are common to both urban and rural localities. Our main interest is in the reduction and, we dare hope, the eventual eradication of these diseases from our population.

Two fundamental aims of a control program are, first, the discovery of cases of syphilis and gonorrhea, and, secondly, placing them under medical care at least until they are no longer infectious. The approach to these objectives depends largely upon the characteristics of the local population and the resources of the community. Ideally, the burden of the diagnosis and treatment of these infections should be assumed by family physicians, or, where it is more desirable, by specialized private practitioners. Frequently, however, economic and social conditions make such an arrangement impracticable. The impoverished condition of many infected persons, who are a potential menace to the community, and the lack of coöperation in others make it necessary for an official agency to share the difficulties of the medical profession, or, occasionally, to invoke the power granted it by law to protect the health of the general population.

As we have amply demonstrated in New York City, it is entirely possible for the medical profession and the Department of Health to function in harmony and to their mutual advantage in the attack on these diseases. I should like to consider briefly, step by step, the essential points in our control program, determined by the needs of the City, and our accomplishments as far as they can be ascertained.

In the latter part of 1935, when our present extensive and intensive campaign against syphilis and gonorrhea was launched, widespread educational measures were adopted. Local newspapers and periodicals joined forces with the Department of Health in urging every one to be examined by a competent physician, and, where necessary, to take treatment. The favorable effect of this publicity is evidenced by the great numbers of telephone and personal requests for advice made to the Bureau of Social Hygiene immediately following each news release. To meet the public demand for information, the Department of Health has utilized all accepted media for the dissemination of knowledge including lectures, film showings, exhibits, and the distribution of posters and pamphlets. During the past year,

* A clinical lecture at the Department of Health in connection with the Twenty-Second Annual Session, American College of Physicians, New York, N. Y., April 8, 1938.

283 lectures and film showings were given to audiences numbering 27,000 persons of diverse social, religious, educational, and family groups.

Professional interest has kept pace with heightened public interest, and, to meet the need that exists in the medical profession for additional training, the Department of Health has made available facilities for instruction. Graduate and undergraduate courses, for groups of 16 to 24 persons at a time, have been given in clinical and public health aspects of venereal disease control. Furthermore, isolated lectures totalling 60 were given in 1937 to professional audiences numbering 6,200. Staff conferences were held periodically during the year, in which outstanding medical authorities participated as guest speakers. These activities are not only informative but furnish an incentive to improved professional performance.

In addition to this general arousing of public and professional interest, more specific methods of discovering cases, and placing and retaining them under medical care were incorporated in our activities. In all its contacts with groups and individuals, the Department of Health, with the aid of the press, has emphasized the desirability of seeking advice and aid from private physicians. The five county medical societies had supplied the Department with lists of physicians competent and willing to diagnose and treat syphilis and gonorrhea at reduced fees; patients are being referred to these doctors at the rate of about 720 a year. As a further aid to keeping patients under the care of their private physicians and clinics, the Department is utilizing Social Security funds to distribute to doctors, free of charge, drugs for the treatment of their syphilis cases. In 1937, about 1,500 doctors and 28 hospitals were supplied with almost 250,000 doses of drugs for about 15,000 patients.

Educational and case-finding activities are centralized under an assistant director in charge of education and epidemiology and four medical epidemiologists. Their functions include, among others, the investigation of sources of infection and contacts of early syphilis cases as well as conferring with private physicians on problems of diagnosis and treatment of their patients. During the year 1937, 745 physicians were visited and 254 sources of infection, contacts, and delinquent cases were brought under the care of these private doctors through the efforts of our epidemiologists. They investigated 434 named possible sources of infection during the year, and of the total, 30 per cent were proved sources of infection. Considering the heterogeneous and rapidly shifting population of New York City, this is considered a creditable record.

As an indispensable counterpart of case-finding activities, a follow-up service must be integrated into a well-rounded syphilis and gonorrhea control program. Cognizance must be taken of the fact that some patients will lapse treatment regardless of attempts to impress upon them the necessity for regular attendance. Precautions should be taken immediately upon commencing treatment to help the patient, where difficulty exists, in removing obstacles which prevent him from continuing regularly under

medical supervision. Where a patient is under the care of a private physician, this function is most satisfactorily assumed by the doctor. In clinics, where a more impersonal relationship must necessarily exist, a specially trained social service staff should be assigned to this task.

However, personal problems often make it necessary for a patient to discontinue treatment. When the patient of a private physician is delinquent, the doctor may request the service of a Health Department nurse epidemiologist to follow up the case for him and under his supervision. The same service is rendered to private clinics whose staff is inadequate for this purpose. This function, as well as the investigation of some sources of infection and contacts, is assigned to a group of eight nurse epidemiologists under the supervision of an assistant director.

During the first quarter of 1938, nurse epidemiologists made 1,740 visits to 943 lapsed cases, sources of infection, and contacts of private physicians and clinics. Of these, 694 were new referrals. The number of referrals from private physicians and clinics rose 62 per cent from 391 in the last quarter of 1937 to 632 in the first quarter of 1938. The use of this service by private physicians and clinics is expanding as they become increasingly familiar with the facilities offered them.

The follow-up for Health Department clinics is being performed by a group of W. P. A. social workers under the supervision of an experienced assistant Bureau director. During the first quarter of 1938, these social workers made 8,624 visits to 6,287 lapsed cases and returned 3,941, or 63 per cent to treatment.

I have considered briefly the measures taken by the Department of Health to discover cases of syphilis and gonorrhea, place them under medical supervision, and to return them to treatment when they are delinquent. In order to round out a well-balanced program, it is necessary to provide diagnostic, consultation and treatment facilities for persons unable to defray the usual expense.

The Department of Health maintains an extensive laboratory service for the examination of blood and spinal fluid specimen for syphilis, and smears for gonorrhea. Fifty-four per cent of the specimens received in the laboratories are sent by private physicians. In 1937, over 430,000 blood and smear specimens were examined; this figure represents an increase of 25 per cent over the preceding year.

At strategic points throughout the City, where the need is most acute, are located 20 centers offering diagnostic and consultation services for private physicians and clinics. When a patient is unable to afford the usual fee for examination, or when it is desirable to have a diagnosis confirmed, or when a consultation is needed, private doctors and clinics are at liberty to use these services. During the year 1937, more than 20,000 examinations of various kinds were performed at these clinics for patients of private physicians and clinics.

Following examination, whenever it is necessary for a patient to be treated, every effort is made to have him continue under the supervision of his family physician or under the care of a doctor recommended by the county medical societies. If this arrangement is impracticable, an attempt is made to send him to a private clinic. If neither of these alternatives is acceptable, the patient is registered at one of the 21 treatment services maintained by the Department of Health. This procedure, as a short statistical analysis will indicate, has proved to be quite satisfactory.

At the end of 1937, the Bureau of Social Hygiene was operating 130 clinic sessions each week (there were 92 at the end of 1936 and 49 at the end of 1935). The most interesting phase of clinic service is that although the number of cases examined during 1937 increased 36 per cent over the preceding year to a total of 67,260 cases, the individuals accepted for treatment increased only 11 per cent in that period. More than three times as many cases were referred by the diagnostic service to private physicians for treatment in 1937 as compared with 1936; the number of referrals to private clinics in that period was almost doubled. The number of patients referred to Health Department clinics for treatment decreased 4 per cent.

Visits to the treatment service increased by 24 per cent, from 350,000 in 1936 to about 430,000 in 1937, although the number of patients registered for treatment increased by only 11 per cent. This fact indicates that clinic patients are now being retained under treatment more effectively than in the past.

In addition to the routine services I have outlined, several projects in medical research and in public health methods in the control of syphilis and gonorrhea are being carried on. The importance of such projects lies not only in the facts which are brought to light but in the stimulating influence they have on the staff of the Bureau and others who are interested in the subject of syphilis and gonorrhea control. Some of these projects are being financed by private funds. The more interesting demonstrations include a project limited to Staten Island which has for its purpose the development and study of educational diagnostic, and epidemiological case-finding methods as applied both to syphilis and gonorrhea. Measurements will be taken from time to time to determine the results of various methods.

In November 1937, funds were made available for further experiment with the massive arsenical treatment of syphilis by the so-called "continuous-intravenous-drip methods" of administering arsphenamine. The details of this study have been planned by a committee of distinguished syphilologists and internists.

Since January 1937, the Bureau of Laboratories and the Bureau of Social Hygiene have been jointly conducting an important clinical and laboratory study of the gonococcus.

These three projects are representative of the interest and participation of the Department of Health in experimental work connected with problems of the control, diagnosis, and treatment of syphilis and gonorrhea.

To recapitulate, the Department of Health is following basic principles, generally accepted as being universally effective in the control of venereal diseases.

The chief elements in the program are:

1. Case-finding activities to include
   (*a*) Popular education,
   (*b*) Epidemiological investigation.
2. Easily available diagnostic services for the general population.
3. Treatment services for low income groups.
4. Follow-up services to retain patients under treatment at least until they are non-infectious.
5. Professional education both for practicing physicians and for undergraduate medical students.
6. Facilities to aid private physicians and clinics in keeping patients under their treatment including
   (*a*) Consultation services,
   (*b*) Free drugs,
   (*c*) Follow-up service.

The success of these measures has, as I have briefly indicated, been encouraging enough to predict that, if the same course of action is followed over a number of years, always with necessary changes to meet current needs, substantial progress will be made in the eradication of syphilis and gonorrhea in New York City.

SYSTEMIC REACTION TO ORAL FUSO-SPIROCHETOSIS WITHOUT LOCAL LESIONS *

By WILLIAM H. BARROW, M.D., F.A.C.P., *San Diego, California*

ORAL spirochetes and fusiform bacilli were first identified in the 1890's as the pathogenic organisms in ulcero-membranous diseases of the mouth and throat. The work of Veillon, Plaut, and Vincent was quickly confirmed by others and thereafter fuso-spirochetal angina and stomatitis were seldom mentioned in the literature except in connection with some unusual or interesting complication or with reference to some new form of treatment. The disease has been called *Vincent's angina* or *Vincent's infection, ulcero-membranous gingivitis, trench mouth,* and *spiro-fusillary gingivitis.* As the nomenclature would indicate the disease has been and is described as being characterized by ulceration or pseudo-membrane formation in the mouth or throat, and even the mildest forms as presenting a definite gingivitis with small ulcerated areas at the gingival margins. In a recent comprehensive monograph on oral spirochetes Smith [1] states that pyorrhea and periapical infection may sometimes be caused by fuso-spirochetal organisms; but even here dental or peridental pathologic lesions are easily demonstrable. Systemic and constitutional symptoms of anorexia, lassitude, cervical adenitis, fever, leukocytosis or pseudo-leukemic dyscrasias are described but only as secondary to the local lesions. The purpose of this paper is to report what appears to be a clinical manifestation of the infection without the characteristic local signs. Although doubtless recognized by many physicians and dentists this form of the disease has not, to my knowledge, been described in the literature.

TABLE I

Symptoms in Order of Frequency

1. Malaise, loss of weight, nervous irritability.
2. Indigestion, anorexia.
3. Aching in muscles of shoulders or neck.
4. Soreness or aching of throat without objective findings.
5. Transient dull red infiltration of buccal mucous membranes, especially of lips.
6. Urticaria.
7. Sensitiveness of teeth with gross or roentgen-ray findings negative.
8. Anemia.
9. Cervical adenitis, "soreness of mouth," angioneurotic edema, gingivitis, fever.

In table 1 are tabulated in order of their frequency subjective and objective symptoms which seem to fit into a definite syndrome pattern. In patients with this symptom complex and where a smear from the gingival margins and from between the teeth revealed spirochetes and fusiform bacilli in abundance treatment effected a disappearance of the organisms and usually brought about relief from symptoms. A recurrence of the bac-

* Read before the General Medicine Section of the California Medical Association at the sixty-sixth annual session, Del Monte, May 2–6, 1937.

terial invasion was accompanied by a return of the symptoms in whole or in part.

In practically all the cases there were complaints of malaise, loss of weight, mental depression, and nervous irritability. The usual causes for psychasthenia were not demonstrable. Intestinal indigestion and loss of appetite were common. The symptoms, however, did not suggest organic disease and gastrointestinal studies were negative. Quite characteristic was a cervico-occipital neuralgia, described as an aching between the shoulders and in the muscles of the neck posteriorly. As common a complaint was an aching in the throat, often with definite spots of soreness to which the patient could point but where careful examination failed to reveal any lesion. A patient with this as the predominant symptom was apt to make his way from one otolaryngologist to another being told in one office that he had "a little sinusitis," in another that he was a psychoneurotic, but himself convinced that nothing could hurt like that without there being something that could be seen. Next in order of frequency was a transient dull red infiltration of the buccal mucous membrane especially of the lips and roof of the mouth. A patient would display this phenomenon with some satisfaction as evidence of the fact that here at last was something that anyone could see, visible proof that his complaints were not all imaginary. This symptom was usually erroneously attributed by the baffled attending physician to overmedication or to a vitamin deficiency. A few of the cases developed urticarias, the possible significance of which will be discussed later. Only about a third of this series of patients complained of any symptom referable to the teeth or gums and this was characteristically a sensitiveness to pressure and to heat and cold. Except in two cases where there was a very mild gingivitis, examinations by competent dentists failed to reveal any demonstrable lesions. It is significant that even when the diagnosis had been established by the finding of Vincent's organisms in great excess in the mouth, it was often difficult, because of the absence of any visible inflammatory reaction to convince the patient's dentist that this could be the etiological factor or that treatment was indicated. As might be expected, a mild secondary anemia occurred in a few cases. There was no leukocytosis such as is often seen in the more severe typical Vincent's infections.

In table 2 the incidence of these symptoms is indicated graphically in a series of 14 patients.

Case 1 presented all the symptoms that have been described except urticaria. In a position to receive the best of medical attention she was studied thoroughly and for two years it was believed that a psychoneurosis was the most probable explanation of her symptoms. Roentgen-rays of the sinuses, teeth, gall-bladder, and gastrointestinal tract were negative. Except for a mild secondary anemia all laboratory findings were normal. Repeated nose and throat examinations were essentially negative. The gums were normal in appearance, free from pyorrhea, and dental examinations were negative. Finally two years after the onset of symptoms there appeared several small ulcers on the pharyngeal wall and buccal mucous membrane which suggested the possibility of a Vincent's infection. Smears from between the

teeth and under the gingival margins revealed the fuso-spirochetal organisms in large numbers. Treatment of the mouth with salvarsan and the oxidizing agents and general treatment with bismuth and neoarsphenamine brought about an immediate remission of symptoms. Recurrences, however, necessitated further treatments until the patient herself called attention to the fact that these recurrences always took place at home, never when she was out of town. Examination then of the rest of the household revealed a carrier (without symptoms) in the person of a maid. With her dismissal permanent recovery was effected.

Case 2 presented all the symptoms previously enumerated except the cervical neuralgia. Her outstanding complaints, however, were a persistently recurring urticaria and a sensitiveness and feeling of looseness of the teeth. In spite of this latter symptom examinations by competent dentists had failed to reveal any demonstrable dental or peridental pathologic lesions. Diagnostic studies by two Eastern internists were essentially negative. Skin tests indicated sensitivity to certain foods

TABLE II

Cases and Symptoms

Symptoms	Cases: Sex and Age													
	I F—40	II F—35	III F—42	IV F—41	V F—48	VI F—47	VII F—46	VIII F—45	IX M—45	X F—60	XI M—55	XII F—55	XIII M—48	XIV M—40
Malaise, loss of weight, etc.	+	+	+	+	+	+	+	+	+	+			+	+
Indigestion, anorexia.	+	+	+	+			+			+	+	+		+
Occip.-cervical neuralgia.	+		+	+	+	+						+	+	
"Aching" of throat.	+	+	+	+		+			+		+			
Redness buccal mucous membranes.	+	+			+		+		+					
Urticaria.		+			+	+		+				+		
Sensitive teeth.	+	+						+					+	
Secondary anemia.	+	+	+			+	+							
Miscellaneous.	Fever	Aggravated with menses	Fever	Adenitis. Ang. neur. edema	Aching mouth. Ang. neur. edema			Gingivitis		Smarting of mouth	Buccal patches. Adenitis		Gingivitis	

but elimination diets gave no relief. On empirical grounds she was treated for a possible faulty calcium metabolism without benefit. It was suspected that this patient's symptoms also were possibly neurogenic in origin. It was only after protracted treatment along these and other lines that a smear was taken from the mouth and a three plus Vincent's infection discovered. This patient was resistant to treatment and although receiving immediate partial relief required several courses of bismuth and neoarsphenamine before recovery was effected. She now reports that she has occasional exacerbations which are easily controlled by local treatment.

Case 3 is the only one of this series which, presenting most of the cardinal symptoms and found to have a two plus Vincent's infection, failed to improve subjectively although the organisms were, as far as could be judged by a smear, eliminated from the mouth. One can only draw the conclusion that the finding of the organisms in a suspected case points to a possible and not to a positive diagnosis.

Cases 4 and 9 are of interest because complaining of their throat symptoms they both for long periods of time sought relief at the hands of otolaryngologists who found no evidence of pathology. It was only when, finally, smears for Vincent's were found to be positive and appropriate treatment was instituted that relief was obtained.

Five cases had urticarias which were relieved or alleviated by treatment after the infection had been demonstrated. In only three of the fourteen cases were there any gross demonstrable lesions of the gums or mucous membranes that might be said to be even suggestive of Vincent's infection. Case 11 had a few small patches on the buccal mucous membrane and a mild cervical adenitis, and cases 8 and 13 had a gingivitis without ulceration or membrane formation. It was only in these last two that the patients complained of any inflammation or irritation of the gums and their inclusion in this series is perhaps warranted on the basis that the other subjective symptoms coincided with those of cases showing no such tell-tale signs, thereby indicating a probable common etiological factor.

The *Treponema vincenti* and the fusiform bacillus in common with other oral spirochetes, spirilla, vibrios, leptothrices, and cocci, are found in small numbers in the mouths of normal individuals. Miller and Epstein [2] in 1926 reported results of smears taken from the gingival margins of 160 mouths in which there was no gross evidence of disease. Spirochetes were absent in only 23 per cent and the fusiform bacilli in only 7 per cent. The organisms were few in about 40 per cent, numerous in about 30 per cent, and very numerous in as many as 10 per cent. They mention other investigators who reported 50 per cent positive smears from apparently normal gingival margins and the finding of fusiform bacilli and spirilla (spirochetes?) in excised tonsils. Obviously then fuso-spirochetal organisms are opportunists rather than primary pathogens, producing characteristic lesions only when favorable conditions for incubation cause them to multiply. Classification of a smear as positive calls for experience and conservatism. Figure 1 showing an occasional spirochete and bacillus is the usual and normal finding. Figure 2 with frequent spirochetes and a few bacilli (a two plus smear) is of possible significance if supported by other clinical signs. Figure 3 with masses of spirochetes and many bacilli is distinctly pathological. The presence of numerous leukocytes in any smear is highly suggestive of an inflammatory reaction even if the gums appear normal. Using this standard as a rough index of the smears from this series of cases, eight were three plus and six were two plus.

Care and thoroughness should be exercised in obtaining the smear. In view of the fact that these organisms are anaerobes a swab wiped over the gingival margins is obviously inadequate. We have used a small platinum loop which is introduced between the teeth and as far under the gingival margins as possible without trauma. It is important that smears should be taken from around and between all the teeth, it being not uncommon to find severe infection in only one part of the mouth.

The question arises as to why the same degree of infection, as indicated by smears, should cause ulcero-membranous gingivitis in one individual, only constitutional symptoms in another, and perhaps no demonstrable reaction in a third. In the case of the mouth lesions any factor that tends to reduce the resistance of the tissues favors the formation and spread of an ulcero-membranous gingivitis. In addition to this is it not possible that there may be much individual variation in a patient's sensitivity to the soluble bacterial toxins or the endotoxins (transient products of microbic proteolysis) and in the character of his manifestation of this sensitivity? The unusually high

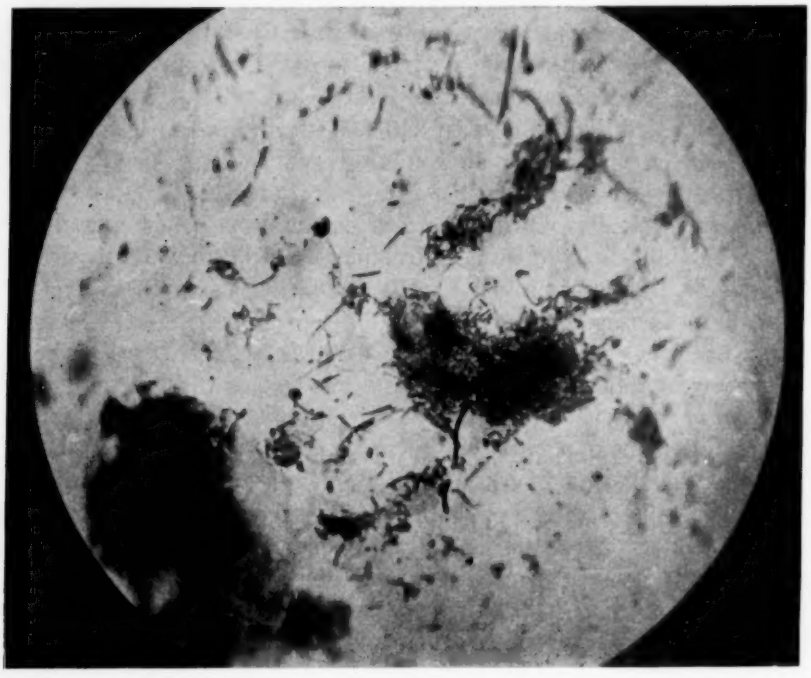

FIG. 1. Smear from normal mouth showing occasional spirochete and a few fusiform bacilli (1 × 1000).

incidence of urticaria in this series might well be evidence of such a phenomenon in these patients. One might advance the theory that there are a few individuals, who with minimal local lesions and maximal systemic symptoms, may be said to be Vincent's sensitive.

It is hardly within the scope of this paper to go into the details of treatment. Certain general principles may, however, be summarized. Fortunately the fuso-spirochetal organisms are arsenic sensitive. The use, therefore, of the arsenicals in local and general treatment constitutes a specific remedy. Bismuth preparations intramuscularly given either alone or in combination with the arsenicals are effective. Kolmer [8] advocates the use

of bismarsen. The *T. vincenti* and the fusiform bacillus being anaerobes, the free and frequent use of oxygen producing agents, such as sodium perborate, is indicated.

Trauma of the gums should be avoided and it is, therefore, well to advise against the use of a tooth brush while the case is under treatment. For the same reason the patient should not, at this stage, be referred to the dentist for scaling of the teeth or other traumatizing procedures. After the infection has been eliminated or brought under control it is, of course, essential that the coöperation of the dentist be sought. Elimination of the so-called

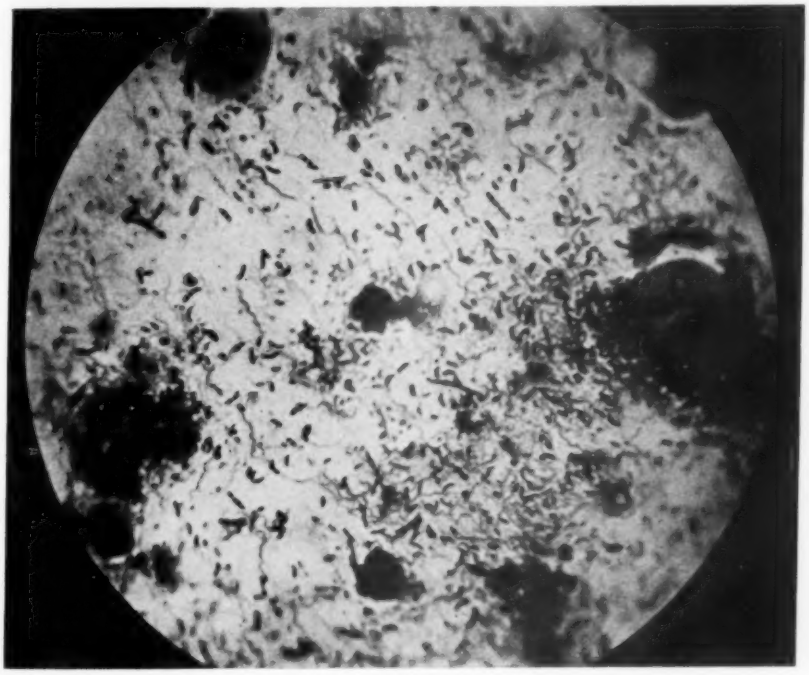

FIG. 2. A two plus smear with numerous spirochetes and fusiform bacilli and a few pus cells (1 × 1000).

"zones of incubation" (abnormalities causing pocket formation or gingival irritation) is often necessary to effect complete recovery or to prevent recurrences. The elimination by the patient of any irritating agents is important. Recently vitamin C deficiency has been mentioned as a possible predisposing factor and this should be ruled out or a vitamin concentrate be given on empirical grounds. Finally the patient's intimate associates should be examined as possible carriers. The Vincent's organisms apparently stimulate no antibody formation. The disease is not, therefore, self-limited and there is no acquired immunity. Susceptible patients consequently require the protection of every possible prophylactic measure.

In the cases reported in this series local treatment alone was prescribed or administered in three and local and general treatment in nine. The teeth were extracted in one case and one case (seen in consultation) was not followed. Of the 14, ten recovered or were markedly relieved after treatment and one case was unimproved (Case 3 previously mentioned). The results in three cases are not known.

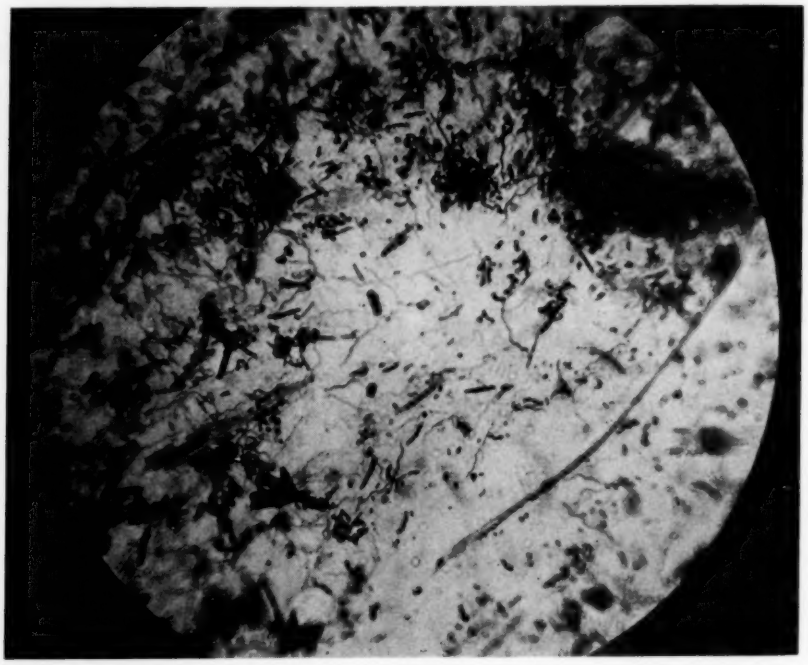

FIG. 3. A three plus smear showing many fuso-spirochetal organisms (1 × 1000).

SUMMARY

1. Vincent's infection as generally described is characterized by an ulcero-membranous inflammation of the mouth or throat accompanied by mild systemic reaction. A series of cases is presented with minimal or no recognizable local lesions but with a definite symptom pattern indicative of infection and toxemia.

2. Smears from around the teeth showed moderate or heavy invasion of fuso-spirochetal organisms and treatment of this condition effected recovery in most of the cases.

3. Vincent's organisms are found in normal mouths so that the criterion of a so-called positive smear is only a comparative one. Care and proper technic in making the smear are essential to a reliable test.

4. The theory is advanced that this atypical manifestation of the infection occurs in individuals who are more than usually sensitive to the organisms.

5. The arsenicals are specific for the treatment of the infection and dental prophylaxis and the elimination of carriers from the patient's environment are necessary for the prevention of recurrences.

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CEVITAMIC ACID (ASCORBIC ACID; CRYSTALLINE VITAMIN C); A CRITICAL ANALYSIS OF ITS USE IN CLINICAL MEDICINE *

By Irving S. Wright, A.B., M.D., F.A.C.P., *New York, N. Y.*

The fact that cevitamic acid can be chemically analyzed, synthesized and recovered from body tissues and fluids has resulted in a tremendous impetus being given to its study. Out of the work already reported (50 to 100 articles per month for the past three years) has emerged a mass of material made up of truths, errors and debatable questions of which the last mentioned group constitutes the major portion.

Four general statements may now be made, however, with reasonable certainty, as follows:

1. Most patients with scurvy can be cured with cevitamic acid. A few seem resistant to this substance whereas they can be cured with large doses of lemon or other citrus fruits.[1]

2. Increased fragility of the capillaries when due to vitamin C deficiency will be restored to normal by the use of this substance, with the same exceptions.[2, 3, 4, 5]

3. Vitamin C deficiency may occur under a great variety of conditions even when the intake of this substance is apparently adequate. These include increased metabolism from infection (with or without fever) or other causes, interference with absorption or utilization because of achlorhydria, colitis or other intestinal disturbances and additional factors concerning which our present knowledge is limited. Deficiency inevitably occurs in man when the intake is inadequate since man is apparently unable to synthesize this substance and his storage capacity is very limited.

4. The proved indications for vitamin C therapy depend primarily on the presence or danger of a deficiency of this substance in the patient. This applies whether the primary problem is clinical or subclinical scurvy or any of the very numerous diseases for which it has been recommended as an important therapeutic aid.

The determination of the degree of deficiency of this vitamin in an individual has given rise to sharp differences of opinion and the presentation of numerous methods and modifications of methods. If one surveys this problem with a broad outlook toward future usefulness it becomes at once apparent that while some of these differences are important, many of them are largely academic.

A recent tendency has been noted to introduce new chemical methods and modifications of earlier methods for the study of vitamin C, which theoretically approach accurate results more closely by minute amounts.

* Presented before the American College of Physicians, New York, N. Y., April 8, 1938.

When, as is the case with certain of these, the procedures used introduce opportunities for errors as great or greater than those of the former technics it appears that the originators are obscuring the situation rather than clarifying it.

The primary purpose of this paper is, therefore, the presentation of a method of approach by which the degree of saturation or deficiency of vitamin C can be determined for clinical purposes. The procedures recommended are mentioned not because they are the only possible methods or because they represent the ultimate but because they have stood well in comparative tests against all other methods, both in our laboratory and other unbiased laboratories. It is expected that improvements will be forthcoming during the next few years.

Probably the simplest procedure giving the maximum amount of information is a single determination of cevitamic acid in the blood plasma. Numerous chemical methods for this have been advocated but we have found the macro method of Farmer and Abt [6] to be very satisfactory. Pijoan and Klemperer [7] introduced a modification of this method using potassium cyanide. Comparative studies of the two technics in our laboratory showed this modification to be unnecessary if the determinations were to be made within 30 minutes but helpful if the blood was to stand four hours or more. The intermediate time zone produced variable results. The normal blood plasma level for cevitamic acid in adults lies between 0.7 and 1.3 mg. per 100 c.c.

This test might be compared to a single blood sugar test. It gives a general idea of the status at the moment of taking the specimen but may have been affected considerably by intake or deficiency of vitamin C during the preceding 24 to 48 hours, or by other factors such as renal retention.[8]

Single urinary specimens may vary so widely in content of cevitamic acid as to be valueless and 24 hour specimens have certain disadvantages as follows:

A. Individual specimens must be analyzed immediately upon voiding or carefully preserved by being acidified to pH_3 with sulphuric or acetic acid and kept in the dark at ice box temperature.[9] Even under these conditions a loss of over 12 per cent may occur in 24 hours.*

B. Twenty-four hour specimens are difficult to secure without loss from ambulatory patients or indeed any but the most coöperative hospital patients.

The obvious solution of this situation was the use of a test dose method. At first doses of 300 to 1000 mg. were given orally.[11, 12, 13, 14] The normal return was considered about 30 per cent in 24 hours, but the possibility of uncertain absorption or utilization from the intestinal tract under certain

* Fleming and Burrows [10] have reported that sulphuric acid destroys ascorbic acid rather than protecting it but for practical purposes we have found its use satisfactory. Our studies do not confirm their extreme statements of rapid destruction by sulphuric acid. We have found sulphuric acid preferable to acetic acid when used in the proper dilutions. Immediate determinations are to be preferred.

conditions indicated the need for an intravenous route of administration. Accordingly we suggested[9, 15] a test dose of 1000 mg. intravenously.* Normally at least 500 mg. are excreted during the following 24 hours. We demonstrated that 80 per cent or more of the total urinary excretion in 24

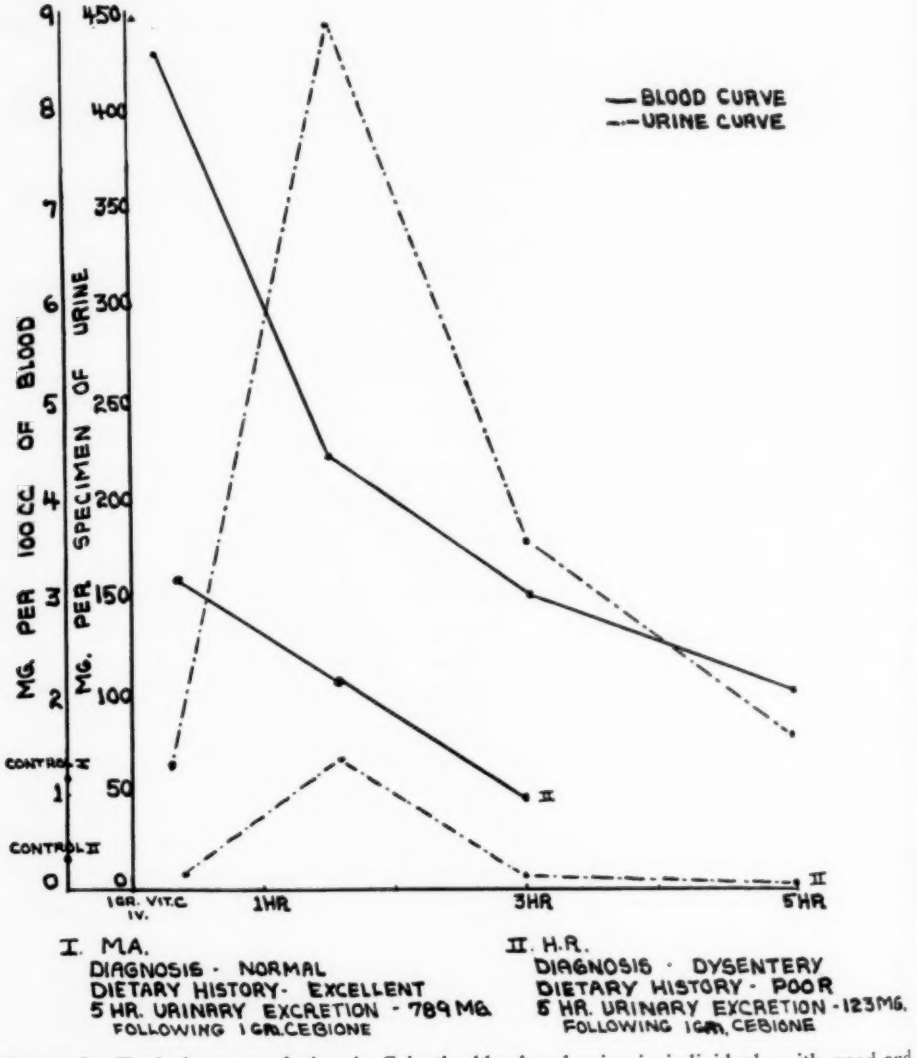

CHART I. Typical curves of vitamin C in the blood and urine in individuals with good and poor degrees of saturation. Following 1000 mg. test dose intravenously.

hours at whatever level would be excreted in the first five hours. This simplified the procedure resulting in a five hour test which could be utilized for ambulatory patients. Similar tests have been advocated using a smaller

* These studies were carried on with cebione (cevitamic acid) which was supplied through the kindness of Merck and Co., Inc., Rahway, N. J.

dosage (100 to 300 mg.). These smaller doses are suitable for infants but have the following disadvantages: *A*. The factor of error of the chemical determinations including that of the endpoint reading is increased as the amount of vitamin C present is decreased. *B*. The effect of the immediately preceding dietary regime may influence the figures proportionately more markedly if the return is small (e.g., 30 to 50 mg. as compared with

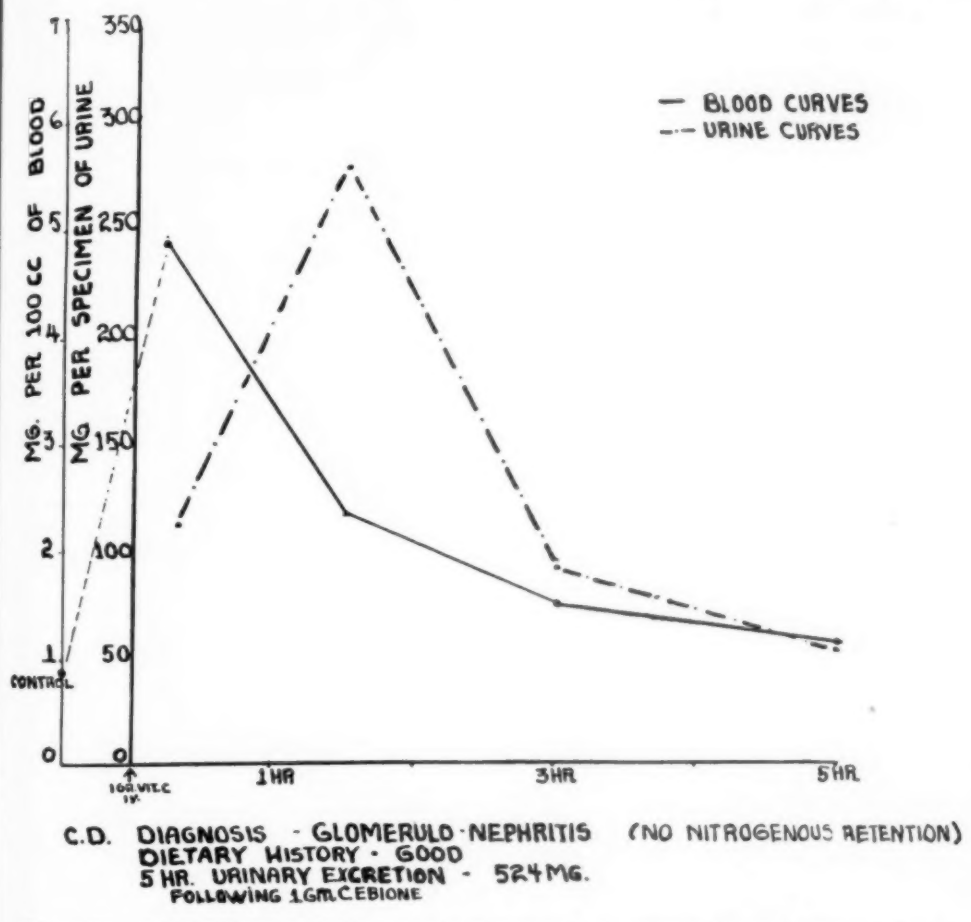

CHART II. Typical blood and urine vitamin C curves in a patient with renal disease but no nitrogenous retention. The curves are normal.

300 to 500 mg.). *C*. The effect of the RSH compounds [16] (interfering reducing substances such as glutathione, cysteine, etc.) becomes proportionately less important with the increase in total figures. We know of no evidence proving that increasing the test dosage produces an appreciable increase in the excretion of these factors.

The test dose of 1000 mg. does produce results which run parallel to certain other methods. For example using the 100 mg. test dose carefully

controlled, about 40 mg. will be obtained as the average output in five hours as against 400 mg. for the 1000 mg. dose from a patient with similar saturation. As above pointed out, however, the larger dose tends to minimize the factors of error. It has been suggested that the large dose method may result in a spilling into the urine even when the body is unsaturated. That this is only in proportion to the saturation has been demonstrated since we

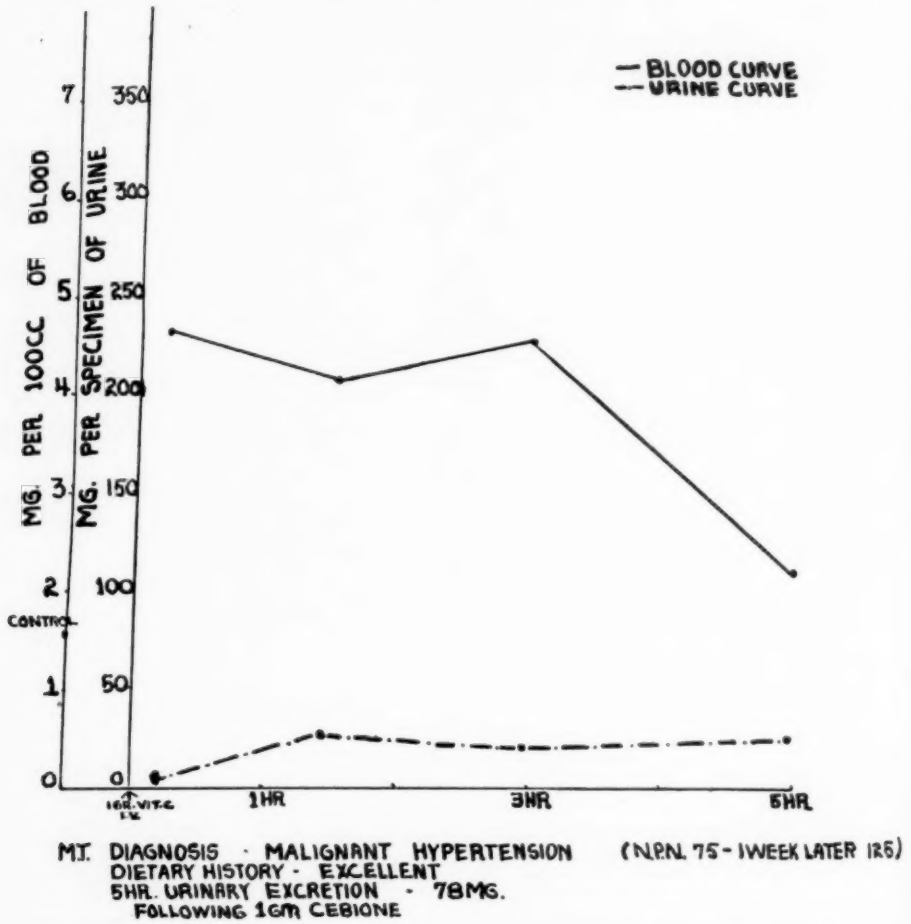

CHART III. Blood and urine curves in a patient with malignant hypertension with nitrogenous retention. Note retention of vitamin C in blood with delayed excretion, only 78 mg. in 5 hours. This does not occur in all patients with nitrogenous retention.

have had excretions as low as 42 mg. in five hours while the blood level dropped to normal probably as a result of rapid utilization or absorption by unsaturated tissues. In saturated cases the return has been proportionally greater, up to practically 100 per cent. In most instances the above outlined determination of the five hour urinary excretion, using a modification of Tillman's dichlorphenolindophenol method, is adequate to establish the

degree of saturation but recently we [8] have demonstrated that in some patients with kidney disease and nitrogenous retention vitamin C retention may also occur. This may interfere with the excretion and hence the interpretation of results from any urinary study. In patients with kidney

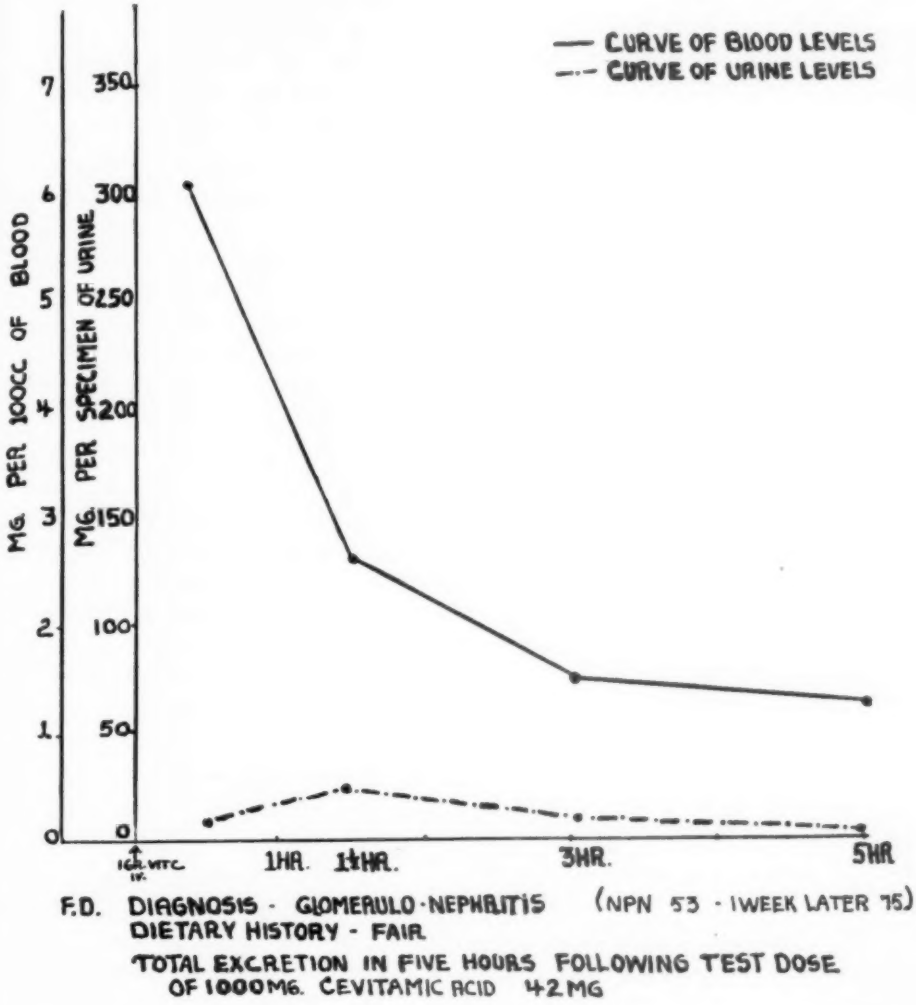

CHART IV. Blood and urinary curves in patient with nitrogenous retention. Note that the blood curve dropped normally without appreciable increase in excretion. We would interpret this as indicating rapid utilization or storage by the body.

disease, therefore, a parallel blood and urinary study clarifies the picture as indicated by the accompanying illustrations.

In addition, one must consider in all chemical determinations other possible factors of error such as the effects of certain drugs, including the

salicylates [17] (not definite) which produce an increased excretion and pyridium [18] which produces a color affecting the endpoint determinations.

We have followed the course of a large number of patients for periods up to two years checking the five hour urinary test against the clinical course of the disease and response to therapy, blood plasma studies and the capillary fragility tests.[4, 9] It has proved to be very helpful and satisfactory for general use. The exceptions to this have been noted.

Mention should be made of the intradermal test of Rotter [19] later reported by Portney and Wilkinson [20] in which the dye dichlorphenolindophenol is injected into the skin and the length of time necessary for the disappearance of the color by oxidation timed. Saturated patients took less than five minutes, normals between five and 10 minutes, and deficient patients more than 10 minutes. Other factors than vitamin C may enter into the reaction but, if confirmed, it appears to have clinical value for rough estimations.*

The value of capillary fragility studies † has been challenged in some quarters. Certain factors have been chiefly responsible for this. 1. The workers expected results which were too exact for most biological tests. The difference of a few petechial spots is not very important but large differences are. 2. Too small an opening was used in a negative pressure type of apparatus. 3. Different areas of skin were used. The latter two factors when combined result in serious error because the potential number of minute vessels capable of rupturing may vary widely in different areas and hence affect the count considerably, especially if small areas are studied. Negative pressure methods require special apparatus, whereas every doctor has in his office adequate equipment to perform a satisfactory and informative capillary fragility test.

The procedure which we have used since 1934 in thousands of observations with very helpful results is as follows: [2, 4, 8]

1. Place blood pressure cuff on upper arm and elevate the pressure to half way between systolic and diastolic readings, maintaining this level for 15 minutes. (If there is an excessive number of hemorrhages the time may be reduced to 7½ or 5 minutes.)

2. Two circles 2½ cm. each in diameter are drawn on the inner smooth surface of the forearm, the upper edges of which should be 4 cm. below the elbow crease. This obviates the great differences found at the elbow. Because of varying numbers of wrinkles, folds, etc., in different individuals, the distribution of the minute vessels is disturbed in that area.

3. Five minutes after release of the pressure the number of the petechiae readily seen with the naked eye are counted and an average taken as the

* Since presenting this paper we have carefully checked this method and found it unsatisfactory, the range of error being too great. Details will be published elsewhere. (Wright, I. S., and MacLenathen, E.)

† Although commonly known as capillary fragility or resistance studies they should more correctly be termed tests for the study of the fragility of the minute vessels of the skin including venules and probably arterioles.

figure. Many new spots appear during the first few minutes after the release of the pressure.

The normal response for adults is 10 or fewer per circle, the borderline zone is taken as 10–20 and above 20 is considered definitely pathological.

4. This may be repeated every four days alternating arms, thus allowing adequate time for restoration of the ruptured vessels. The negative pressure methods do have the one advantage that the tests may be repeated more frequently.

This simple procedure, a modification of Gothlin's technic,[21] used routinely will uncover a surprising number of individuals with pathological fragility of the minute vessels. The fact that this is not always due to scurvy makes the observation none the less important. In spite of all of our chemical procedures to determine saturation *fragility of the minute vessels still remains the first positive clinical evidence of the presence of the disease entity scurvy.*

The fragility may also be increased in other conditions such as certain purpuras; in poisonings, such as those due to neoarsphenamine and carbon monoxide; by toxins, such as those of scarlet fever, subacute bacterial endocarditis, and diphtheria; and by metabolic products associated with anemia, acetonemia, menstruation and other conditions. In many of these conditions increased fragility occurs as a preclinical sign and its presence should place the physician on his guard. A clinical differential diagnosis is usually easily made. The confirmation by chemical tests and a cure with cevitamic acid establishes the clinical diagnosis of scurvy. On the other hand the chemical tests may be deceiving in this situation, since lack of vitamin C may quickly result in unsaturation without the development of scurvy for weeks or months and conversely a high vitamin C diet given to a patient with scurvy may produce a rapid chemical recovery while he still has clinical manifestations of the disease.

One of the most important facts which has been established by all workers in this field is that scurvy, especially in its preclinical forms, is a very common disease among all economic classes. It would be a safe generalization to make that practically every physician occasionally has had one or more of these cases pass through his office or clinic unrecognized. Use of the capillary fragility test above described would have resulted in the recognition of most of these cases. The symptoms of which these patients may complain vary enormously, including weakness; heaviness; pains in the legs and elsewhere; dizziness; nausea; dyspnea; bleeding from nose, mouth, rectum and bladder; easy bruising; and a host of others. The signs are also of a most diverse nature, including bleeding of the gums, throat, nose, urinary and gastrointestinal tracts; purpuric spots and evidence of rupture of the vessels anywhere on the body surface including under the toe nails, the vessels of the sclerae and other unusual places, brawny pigmented edema of the lower legs and many other bizarre manifestations, practically all of

which depend directly or indirectly on rupture of the blood vessels. Roentgen-rays may show elevation of the periosteum from hemorrhage but in our experience this is rare in adults as we see the disease today.

In our series of more than 200 cases of definite scurvy we have seen five cases in doctors or their families and eight cases in nurses. More than 50 per cent of our patients could easily afford the preventive citrus fruits, many were wealthy and one owned a large orange grove. The causes of the disease aside from poverty were, distaste for citrus fruits and other food containing large amounts of vitamin C; allergic and gastrointestinal sensitivity to such foods; diets prescribed by physicians for the treatment of ulcers, colitis, urticaria and other conditions; faddist diets; winter diets and inability to utilize vitamin C when taken by mouth. Cases in these groups constitute one major established indication for the use of cevitamic acid.

The list of diseases for which cevitamic acid has been recommended is too long to permit a detailed discussion of each claim. Many have been mentioned in our previous reviews.[4, 8] Only those which seem significant at present will be included in this paper.

While certain patients with low platelet counts seem to respond to this therapy, and hence might be classified as scurvy, the great majority of patients with the typical syndrome of thrombocytopenic purpura receive no benefit from its use even in massive doses.[4] Hemophilia likewise is not helped in our experience.[4]

It has been possible to establish according to various workers that in many diseases with infection, with or without fever, a marked deficit of vitamin C does occur. Such is especially the case in pneumonia,[22, 23, 24, 25] tuberculosis,[26, 27] rheumatic fever and rheumatoid arthritis,[28, 29, 30] whooping cough,[31] and osteomyelitis.[32] This should not be construed as proving an etiological relationship in these conditions or as establishing any curative value for the use of cevitamic acid in such cases. It is, however, logical to attempt to replace this deficit, bringing the vitamin C content of the tissues up to normal as a matter of supportive therapy. Although encouraging therapeutic results have been reported in the treatment of intestinal tuberculosis,[33] whooping cough,[31] and diphtheria [34, 35] (especially combined with antitoxin), the preliminary paper by Gander and Niederberger [25] of Switzerland reporting their results following the use of massive doses in pneumonia is the most startling and hence in the greatest need of rechecking by other workers. By overcoming the total deficit (1000 to 2000 mg.), usually present in pneumonia cases, in the first 24 hours they reported striking drops in the temperature curves similar to those obtained by serum therapy while the signs persisted for several days, as is also often seen following serum therapy.

Animal experimental studies have suggested that vitamin C might be of aid in the prevention and treatment of poliomyelitis [36, 37, 38] and in the

encouragement of wound healing [39, 40] but conclusive proof of its value in the clinical handling of these conditions is as yet not available.

As a preventative against the development of secondary prescorbutic or scorbutic conditions we must in all diseases be careful to include an adequate supply of vitamin C in the diet. This is especially important where the intake is usually low as in diseases of the gastrointestinal tract and where the utilization is high, as in fever. When fruit juices are contraindicated cevitamic acid should be given and when not well utilized by the oral route it should be given intravenously or intramuscularly.[41]

Evidence has been slowly accumulating which leads us to believe that there may be ingredients in citrus fruit and in other food substances which may play a part in helping to control certain types of hemorrhage but which are absent in the synthetic preparations of cevitamic acid. Occasional cases have been noted by various workers, including ourselves, which do not respond to synthetic vitamin C but which respond to lemon juice or to an equivalent natural source.

In addition two other substances which may be termed vitamins (at least until more complete studies have been carried out) have been described by Dam [42] and his coworkers and Rusznyak and Szent-Györgyi.[43] These substances, both of which appear to have antihemorrhagic properties, have been termed vitamins K and P respectively. Butt, Snell and Osterberg [44] have reported encouraging results from the use of vitamin K together with bile or bile salts in the treatment of jaundice very recently, but all of the work with these substances is in a very preliminary state and it cannot be considered that they are of established value at present.

Dosage

The curative and maintenance dosage of cevitamic acid is in most instances between 30 to 50 mg. per day orally. This varies greatly, however, and we have had patients in whom 1000 mg. daily given by mouth failed to cure the scorbutic condition. This must have been due to faulty absorption from the gastrointestinal tract since intravenous administration produced rapid cure. Schultzer [45] produced evidence that at least in a small group of patients the results were as rapid using a dose of 40 mg. as when 600 mg. daily orally were given. We have had patients in whom less than 1000 mg. doses intravenously failed to prevent the recurrence of scurvy. In some instances we have been so far unable to fully explain this experience.

Fortunately the toxicity of this substance is low so that overdosage does not appear to be harmful. Experimentally we have given as high as 10,000 mg. intravenously in a single dose to one man and have given 1000 mg. daily for many months intravenously without untoward effects, the excess beyond saturation being excreted.

The dosage for clinical use may range, therefore, between 30 and 1000 mg. orally, or intravenously, and up to 100 mg. intramuscularly each day without danger.

Comments

It should never be forgotten that scurvy is a common disease and a common complication, easily missed, easily diagnosed and easily cured.

Our present knowledge leads us to conclude that the indications for the use of cevitamic acid in medicine are dependent on the demonstration of a deficit or the danger of a deficit of this material in the body, whatever may be the cause or the disease involved.

The use of tests for the vitamin C content of the blood, saturation tests with urinary determinations, and the capillary fragility tests will give a fairly complete picture of the state of vitamin C metabolism for clinical study.

In the absence of facilities for chemical studies cevitamic acid may be administered safely on the basis of the suggestions outlined in this paper.

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CLINICAL AND HEMATOLOGICAL REVIEW OF SPRUE BASED ON THE STUDY OF 150 CASES *

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MANSON described sprue as "an insidious chronic remitting catarrhal inflammation of the . . . alimentary canal occurring particularly in Europeans who are residing or have resided in tropical or subtropical climates." Certain investigators, such as Newham, Morris and Manson-Bahr [1] stress the fact that the anemia of sprue is secondary to a gastrointestinal lesion and not due to disease of the blood-forming organs. The disease, however, is classified in some of the standard textbooks under Diseases of the Hematopoietic System and in others it is included under Gastro-Enterology. Now, is sprue primarily a disease of the alimentary canal or a blood dyscrasia?

By presenting the data gathered during a study of 150 cases we shall endeavor especially to clarify this fundamental issue. No attempt will be made to discuss all aspects of the disease.

ANALYSIS OF THE SERIES

The present series is made up of 150 persons all but two of whom are natives of Puerto Rico. There were 121 whites, 26 mulattoes, and only 3 negroes. The ages ranged from 9 to 84 years. One-third of the patients were less than 40 years old, a point of difference from true Addisonian anemia.

In general appearance certain of our older patients presented strong resemblances to persons with pernicious anemia. Loss of subcutaneous fat, and wrinkling and pigmentation of the skin, especially on the arms and legs, favor the diagnosis of sprue. In contrast to pernicious anemia the spleen was always normal or small. Although purpuric or scorbutic spots were occasionally found, retinal hemorrhages were uniformly absent.

Students of non-tropical sprue, such as Hansen and Staa,[2] have emphasized the occurrence of tetany, osteoporosis and osteomalacia. Our tropical experience has included occasional instances in which there were decalcified areas in the costal cartilages. We have never found osteoporosis, osteomalacia or tetany.

ETIOLOGY

Our studies do not support the opinion that sprue is contagious. We did find, however, that in 75 per cent of the cases in which a reliable history could be obtained sprue or pernicious anemia had existed in one of the patient's parents, usually the mother. We therefore believe that a hereditary factor is present.

* Delivered before the American College of Physicians, New York City, April 7, 1938.

Of the many theories of the etiology of sprue only the concept of a deficiency disease has been able to withstand prolonged investigation. Castle, Rhoads and their collaborators [3] while working in Puerto Rico confirmed the belief that deficient diets frequently antedate the onset of clinical sprue. They demonstrated that feeding of the vitamin B complex, in the form of autolyzed yeast, produces reticulocyte crises and improvement of the blood picture in certain cases. The intrinsic gastric factor was found lacking in other instances and some of the more severe or advanced cases showed an apparent defect in absorption from the intestinal canal. Castle states " it is probable that the usual type of diet is such as to favor a diminished consumption of some of the known sources of the extrinsic factor, such as meat, eggs and whole grain cereal." Recent unpublished analyses by the Chemistry Department of the School of Tropical Medicine * definitely established that the Puerto Rican diet is inadequate in vitamin A, low in calcium and phosphorus, low in fat and high in carbohydrates. The protein is sufficient quantitatively but is poor in quality. The amount of iron was found to be higher than in the normal continental diet.

A comparison between the average continental diet (2400 calories) and that of the Puerto Rican peasant or " jibaro " follows:

	Continental	Puerto Rican
Vitamin A	7895 Units	1220 Units
Calcium	0.35 Gm. per 100	0.29 Gm. per 100
Phosphorus	1.25 Gm. per 100	0.73 Gm. per 100
Proteins	55 Gm.	58 Gm.
Fats	98.97 Gm.	61.70 Gm.
Carbohydrates	321.33 Gm.	400.54 Gm.
Iron	0.021 Gm. per 100	0.032 Gm. per 100

This most inadequate diet has been taken steadily since childhood by many of the sprue patients, true enough, but it has also been taken by nearly all those suffering from hookworm infestation. Yet both clinically and hematologically the hookworm anemia differs from that of sprue. The former is invariably hypochromic, microcytic or normocytic; the latter is typically macrocytic. Diet therefore is far from explaining the whole story.

Circulatory System

It is well known that deficiency of vitamin B may affect the heart. Since the Puerto Rican diet is probably deficient in vitamin B and since the administration of vitamin B has been beneficial in sprue, special studies were made of the circulatory system in our patients. Twenty-five untreated patients were selected at random from the group. The venous pressure and circulation time were normal. The cardiothoracic ratio averaged 44 per cent, and in only one instance exceeded 50 per cent. The vast majority of the patients had a vital capacity from 200 c.c. to 1200 c.c. below normal. In our series the blood pressure was low. It should be mentioned, however,

* Personal communication of Dr. J. Axtmayer.

that a general response to treatment has usually been accompanied by a gradual rise of pressure. In a few cases definite hypertension and left ventricular preponderance appeared.

Metabolism and Digestion

Studies of gastric secretion revealed almost universal hypochlorhydria or achlorhydria, despite the injection of histamine.

Investigations of glucose tolerance proved especially fruitful. Virtually all our patients had low fasting blood sugar values. The ingestion of 75 gm. of glucose usually did not raise the glucose level by more than 15 mg. per cent. In most of the younger patients the glucose curves returned to normal as the disease yielded to treatment. This agrees with the findings of Thaysen. Five of our older patients, however, retained flat glucose curves after complete recession of the clinical and hematologic abnormalities and despite continued injections of liver extract. This seems to show that the gastrointestinal tract may remain permanently damaged in occasional cases.

As already observed by Hanes[4] our blood sugar curves were high when glucose was administered intravenously. This fact, together with the observations of Barker and Rhoads,[5] favors the theory of deficient intestinal absorption and tends to make the hypothesis of pancreatic disease less important in our understanding of sprue. The pancreas was found to be normal in 18 of 20 cases studied at autopsy.

The late lamented Thaysen[6] of Copenhagen declared that celiac disease, non-tropical sprue, and tropical sprue are one disease. He set forth the following features as characteristic: (1) Abnormal excretion of fat in the feces, (2) normal or slightly increased fecal nitrogen, (3) flat blood-sugar curve, (4) increased basal metabolism. He stated that these four metabolic disturbances were conjoined in no other disease. He regarded their presence as proof that the aforementioned diseases are identical.

We grant that steatorrhea and flat glucose curves occur regularly in tropical sprue. Nitrogen determinations have not been made. Studies of the remaining criterion—namely, basal metabolism—do not support Thaysen's contention, but show instead a low level of metabolism. In 10 typical cases selected at random the readings ranged from plus 4 per cent to minus 23 per cent.

Blood and Bone Marrow

The blood was studied by the methods of Wintrobe. With the exception of one atypical case the lowest mean cell volume in the series of 150 cases was 102 cubic microns, the highest was 220 cubic microns, and the average for the series was 123.6. The color index was below one in 23 cases. The highest index was 2.2, the average was 1.22. The volume index was never below 1.0; the maximum was 2.3, the average was 1.39.

The mean cell hemoglobin varied between 26 and 59 micrograms, with an average of 36.6. The mean cell hemoglobin concentration was found at 22 per cent or lower in four cases, the lowest figure being 20 per cent. The highest was 45 per cent, the average was 26.1 per cent.

The hemoglobin averaged 66 per cent. The erythrocytes ranged from 690,000 to 4,410,000 per cubic mm., with an average of 2,710,000. Leukocytes ranged from 1,550 to 13,600, the average being 5,280.

Thus the anemia was found to be macrocytic, usually hyperchromic, occasionally hypochromic, very rarely normocytic, never microcytic.

With the possible exception of one case reported by us [7] (Revista Medica de Barcelona), in all cases of a microcytic hypochromic anemia the diagnosis of sprue has failed the test of thorough clinical and anatomical investigation.

Our studies of the sternal marrow yielded new and significant data. Observations were made by the aspiration method of Osgood and Young in 40 cases. Of these we shall use only 28 in which material was obtained before treatment and again 10 days and 2 months after the first injection of liver extract. Differential counts were made from smears of aspirated marrow stained with Jenner-Giemsa; 500 cells were counted in each smear.

Megaloblasts were frequently seen. Usually there were more erythroblasts late or early than normoblasts, but only in five cases did megaloblasts outnumber the normoblasts. Megakaryocytes, plasma cells and monocytes were very rarely seen. The lowest megaloblast count was 0.2 per cent, in a case showing very few erythroblasts and a relatively high proportion of normoblasts. The highest figure for megaloblasts was 23.4 per cent. This case showed 12.2 per cent early erythroblasts, 9.8 per cent late erythroblasts, and 8.6 per cent normoblasts.

The following table (table 1) portrays the average differential counts of the aspirated marrow in 28 cases. It will be observed that the megalo-

TABLE I

Sprue

Sternal Marrow (500 cells counted)	Initial	10 Days	2 Months
Megaloblasts	6.31	1.79	0.60
Erythroblasts (Early)	8.71	3.06	1.17
Erythroblasts (Late)	11.12	5.23	2.80
Normoblasts	15.59	11.68	11.26
Myeloblasts	.72	1.24	0.63
Pro-myelocytes	2.60	3.53	3.40
Myelocytes (Neut.)	17.83	16.46	17.51
Myelocytes (Eos.)	2.77	3.54	2.51
Myelocytes (Baso.)	0.30	1.78	0.40
Polynuclears (Neut.)	26.92	44.14	51.91
Polynuclears (Eos.)	1.91	1.26	2.43
Monocytes	0.03	0	0
Lymphocytes	5.11	5.95	4.89
Megakaryocytes	0.07	0.24	0.06

blasts gradually declined to the low level of 0.6 per cent after two months of treatment, while the neutrophilic granulocytes rose from 26.92 per cent to 44.14 per cent in 10 days, reaching 51.91 per cent at the end of two months. The erythroblastic elements decreased from 41.73 per cent to 15.83 per cent in two months. At the same time the myeloblastic element rose from 53.05 per cent to 78.79 per cent.

In three cases we were able to observe marked hematologic changes in the marrow three days following the first injection of liver extract, before any signs of regeneration could be detected in the peripheral blood and before any improvement had occurred in the symptoms. In one of these three cases (table 2) a rapid maturation of megaloblasts was taking place. Within three days the proportion of megaloblasts fell from 23.4 per cent to 12.2 per cent. Early erythroblasts fell from 12.2 per cent to 8.8 per cent. Late erythroblasts rose from 9.8 per cent to 23.2 per cent and normoblasts rose from 8.6 per cent to 28.8 per cent.

TABLE II

Sternal Marrow (500 cells counted)	Initial	Third Day
Megaloblasts	23.4	12.2
Erythroblasts (Early)	12.2	8.8
Erythroblasts (Late)	9.8	23.2
Normoblasts	8.6	28.8
Myeloblasts	.6	0
Pro-myelocytes	2.0	.6
Myelocytes (Neut.)	12.4	7.6
Myelocytes (Eos.)	2.2	2.0
Myelocytes (Baso.)	.2	0
Polynuclears (Neut.)	18.2	13.8
Polynuclears (Eos.)	2.8	2.0
Monocytes	.4	0
Lymphocytes	7.0	1.0
Megakaryocytes	.2	0

IS SPRUE PRIMARILY A DISEASE OF THE GASTROINTESTINAL TRACT?

The prominence of the gastrointestinal manifestations in sprue and the recurrence of cramps and diarrhea in some cases after complete hematological improvement has taken place are circumstances which have led to the belief that the disease is primary in the gastrointestinal tract. On the other hand it is our impression that patients suffering from anemia rarely apply for treatment until the disease is far advanced. In contrast with this, patients who have diarrhea are more apt to apply for early medical attention.

We have had occasion to study very early cases of sprue—cases of one to two weeks' duration. Examination invariably showed the presence of macrocytic anemia and of megaloblastic bone marrow. Still more convincing are the cases which have shown only a macrocytic anemia for weeks and months prior to the appearance of the typical glossitis and digestive disturbances.

Additional evidence lies in the fact, previously mentioned, that after liver therapy maturation of the megaloblasts in the marrow occurs before the digestive disturbances begin to improve.

Treatment

Unquestionably the two most important factors in the treatment of sprue are an appropriate diet and adequate liver therapy. Ashford insisted on the necessity of a high-protein, low fat and low carbohydrate diet, and his opinion has been confirmed by almost all the physicians of Puerto Rico. Miller and Barker [8] state that "The maintenance of a diet for sprue in addition to liver therapy gives a patient more complete relief from gastrointestinal symptoms than does liver extract alone."

In the older patients, in whom more or less permanent gastrointestinal degeneration has occurred, liver extract even in large doses has usually failed to abolish the diarrhea unless a strict dietary regimen is followed.

In previous communications [9, 10] we have reported the therapeutic failure in sprue of certain preparations which had been considered potent in the treatment of Addisonian anemia. Ventriculin, Extralin, and Autolyzed Liver Extract have failed in sprue. The failure cannot be attributed entirely to deficient absorption, for in some cases aqueous liver extract (Valentine) has been successful. The highest reticulocytosis observed in sprue (65 per cent) occurred in a patient who received aqueous liver extract "per os" after full doses of Ventriculin during 15 days had shown no effect.

Lilly's number 343 (Castle's formula) is a relatively crude or diluted extract, high in ash. It contains much inert material and probably carries with it an appreciable amount of what we might call the B_2 complex. Without doubt it is highly effective in the treatment of sprue anemia. Lack of response of this anemia to a concentrated extract as contrasted with positive response to the cruder extract, if demonstrated, would therefore serve to differentiate sprue from Addisonian pernicious anemia and to establish B_2 hypovitaminosis as the most important factor in the etiology of sprue.

This idea was tested in 70 cases. Five patients received a single 2 c.c. dose of Lederle's concentrated extract intrasternally. The resultant reticulocytosis averaged over 20 per cent, and the glossitis rapidly disappeared. The other 65 patients received intramuscular injections of 1 c.c. daily for three days, then every third day for one month, then every five days for one month, a dose larger than that recommended for pernicious anemia. Sprue is more resistant than pernicious anemia and requires larger doses of liver. The highest reticulocyte response occurred in the most anemic patients.

We obtained a higher reticulocyte response using diluted extracts in the group of patients having initial red cell values of less than a million. In all other groups the response to the concentrated extract compares favorably with that produced by other crude extracts and also with the American Medical Association's standards of potency in pernicious anemia.

Thus, liver concentrate is highly effective in all cases of sprue characterized by macrocytic anemia, whether hyperchromic or hypochromic.

Four patients in the present series of 150 showed definite evidence of spinal cord involvement. In each case the neural symptoms improved under treatment.

In Puerto Rico the death rate from sprue is 65 per million inhabitants. This rate has not changed in recent years.

Conclusions

1. A clinical and hematological survey of 150 cases is presented.
2. It is evident from this survey that there is a definite racial predisposition and a probable hereditary factor in sprue.
3. Bony changes, reported by European and continental American investigators of sprue, were not found in this series.
4. The basal metabolism, studied in 10 cases, was found to be low.
5. Since Puerto Rico is a tropical island in which diarrheal diseases are prevalent the glucose tolerance test must be used for prognosis rather than diagnosis in Puerto Rican cases of sprue.
6. The most constant laboratory finding is macrocytic anemia usually hyperchromic, occasionally hypochromic, with a megaloblastic type of marrow.
7. We are inclined to regard sprue as primarily a disease of the hematopoietic system, not of the gastrointestinal tract.
8. Despite its low vitamin B content, concentrated liver extract was found to be highly beneficial in the treatment of sprue, including cases with spinal involvement.
9. The death rate from sprue in Puerto Rico is estimated as 65 per million inhabitants per year.

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THE SOCIAL RESPONSIBILITIES OF MEDICINE *

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THE social responsibility of medicine, as I see it, is to provide to all classes of the population medical care of the highest quality. A lesser adjective like adequate is so indefinite that it can be argued out of all meaning. It is hardly necessary to say that any program that professes to provide the highest quality of medical care must include measures for its continuous improvement.

This premise may be challenged on the grounds that members of the medical profession have no greater moral responsibility to the public than do men and women in other walks of life; that medicine can not be reorganized apart from the rest of the social structure; and that, in any event, it will advance best under the laissez faire principles of free competition. Granted that all professions or trades have an equal responsibility, there is no reason why medicine should not lead the others in the discharge of duty. As to laissez-faire principles of free competition, they are abhorrent to the traditions of medicine with which we its priests have taken such care to inculcate the multitude. In its baldest terms this tradition holds that medicine is not a mere commodity to be sold competitively at the highest price and that its dispensers are not simply salesmen free to employ all the advertising tricks of the hawkster. We employ the bedside manner, not the sales manner; our personal relations are all sacred, not carnal; our art of medicine is a supplement, not a substitute, for science. Medicine can not have its cake and eat it. If it insists on its unique altruism and solicitude for the public weal, the public will take it at its word. I may seem just now to have ridiculed some of the concepts that many of you cherish. It is not the concepts, but the clichés in which they are expressed and certain implications of these clichés that drive me to ridicule. During the last few months my attention has been much directed to certain defenses of the present system of medical practice. The most recurrent arguments are declarations of good-will and the satisfactory state of existing conditions; assertions that those who labor in the making and teaching of medicine know nothing of its application; and claims that all incentive to labor and all the human amenities will vanish if an individualistic relation between patient and physician, involving personal payment in the coin of the realm, is abolished. At this point I must confess some prejudice. Confronted with the dictum that the scientific investigation of medicine is incompatible with its clinical application I am at a loss whether to forsake laboratory or clinic. When, in addition, I learn that the full time man has no incentive for work and can not establish with patients the personal relations that are essential to the proper conduct of medical practice, I am constrained to drop both. Fortunately

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at this juncture I am reminded that the realistic humanity of the salaried trained social worker is infinitely more effective in the diagnosis and treatment of social ills than the conditioned sentimentality of the high-minded ladies I remember in my father's parish.

The most distinctive feature of our era is the enormous technological advances that have come from the rapid development and exploitation of scientific discoveries. One of the inevitable consequences of this has been the substitution for individualistic enterprise of large organizations which can assemble and coördinate the skills and facilities necessary for production under the new system. Medicine as a whole has evaded this movement, in spite of the fact that it has been greatly affected by technological advances. Modern methods of diagnosis and treatment require a breadth of knowledge, a mastery of technic and material equipment that no one man can hope to possess. And if he did possess them he could not profitably exploit them by his own undivided efforts. In addition science is marching with an ever accelerated tempo that makes it impossible for a single individual to keep abreast of its advances in the whole field of medicine. In the face of these facts it is mawkishly sentimental to bemoan the loss of the physician who practised all branches of the healing art.

It is absurd to argue that, because most ailments are trivial and can be treated without special skill or equipment, experts with modern facilities need be available only for exceptional cases. It is the detection of these exceptional cases that demands the highest powers of discrimination. The increasing complexities of medicine have led its practitioners more and more to specialize. Since there is no other means of securing expert service this tendency to specialization cannot and should not be checked. However, although almost any technical procedure can be mastered by persons with moderate intelligence and average dexterity, something more than these attributes is needed to guarantee the intelligent application of this technical skill. Society must be assured that technical proficiency is not exercised for its own sake, but only under the control of responsible judgment. In other pursuits, confronted with the same problem, a solution has been found in organization. Some similar coördination of medical services would seem to be desirable, if not inevitable. Group practice, a device for securing such coördination in an individualistic system, is unfortunately more certain to achieve economy and profits than high quality of service. Moreover, its benefits must be largely confined to the self-supporting class.

To provide the highest quality of medical care for every person, modern facilities for diagnosis and treatment, in the hands of capable personnel, under competent direction, must be universally available. The cost of such a program under the present system would have to be borne by the patients as individuals. It is self-evident that none of these costs can be met by the poorest members of the population. This class which can not pay for its medical care is larger than the class which for general purposes is termed indigent. Medical costs are occasional, not continuous like the

prime necessities, food, clothing and shelter; they may vary from nothing to an indefinite amount and cannot, therefore, be budgeted with accuracy. In addition the disabilities of illness impose a double burden: the cost of medical care proper and the loss of earning power. In illness increased costs coincide almost invariably with diminished income; the otherwise self-supporting individual may at any time be reduced by illness to the indigent class. It is forever to the honor of the medical profession that its members have uniquely recognized their responsibility to serve gratuitously those who can not afford to pay. It is, however, fundamentally inequitable for society to accept these services without remuneration, and it is economically impracticable for physicians to offer them. Proper care consists no longer of purely personal services; it involves the purchase and maintenance of expensive equipment. If the physician is to provide these facilities free to some patients, he must be remunerated by others. The ultimate burden of his charity falls only partly on himself, partly on his more wealthy patients, who therefore pay an extra penalty for illness. Furthermore, unless these supercharges are sufficiently large the highest quality of service can not be maintained. The burden of caring for the indigent must be distributed so that it falls equitably upon the whole population. I believe this is possible only if it is transferred to the government. Philanthropy, even if it takes the form of community chests, is too casual and penalizes virtue and generosity. If, however, the community is to assume the burden of caring for the indigent, it has the right to demand that the medical care it subsidizes be both economically and efficiently administered. Personnel must be carefully selected, responsibility and duties properly allocated, and equipment and facilities centralized to obviate unnecessary duplication of effort and materials.

Above the medically indigent is a larger group, probably the largest in the population, which can pay something for medical care. The number who can actually assume the total costs depends entirely upon the standards which are set. This number can be increased if either the incidence and duration of disability or the costs incurred through this disability are met collectively. This is the argument for medical coöperatives and contributory health insurance. With the general trend towards social security legislation, I personally believe that some form of health insurance is likely to be imposed upon us. If we are to have unemployment insurance there is no reason why unemployment through illness should not be compensated just as much as unemployment arising from faults in the economic structure. For the relief of this purely economic aspect of ill health, insurance may be a necessary and beneficial social expedient in which the interest of the physicians is no greater than that of any other body of citizens. When, in addition, insurance includes the provision of medical services, the interests of the medical profession are directly touched. In those countries in which compulsory health insurance has been introduced it has vindicated itself inasmuch as it has insured wider distribution of existing medical

services to the class to which it applies with more certain compensation to physicians who practice under its provisions. Nevertheless it is not a panacea for the ills of the medical system. Contributory insurance, especially when it is confined to that class which is on the precarious margin of economic competence, can not provide medical care of the highest quality nor does it promise anything for improvement of quality. It offers nothing to the truly indigent and is entirely inapplicable to thinly populated areas.

I have dwelt particularly on health insurance, not because of its intrinsic importance to my theme, but because it illustrates a general error that vitiates the formulae that have been proposed for the solution of the problem of popular health. Whether these emanate from lay or medical sources all are apparently predicated on the assumption that the medical profession is built on the lines of the medieval guilds with physicians holding the position of the artisans of a previous era. Actually, however unpleasant it may sound, in this respect too, medicine has been transformed quite as relentlessly as have all activities that have their roots in science. The practitioner has fallen almost completely into the derivative position of distributor or dispenser. The productive services of medicine have been largely taken over by educational and research institutes and hospitals. No program for the improvement of medical care that considers only the distributors to the neglect of these productive services can be satisfactory. It is a little tiresome to hear from our professional publicists of medicine that only practitioners have any comprehension of the problems of medical care.

A first class medical training has now become more costly than any other kind of education. The students can bear only a small and diminishing proportion of the expenses. The high school education, which used to provide a satisfactory background, must now be supplemented by a carefully selected college course. This must be followed by four years of medical school and at least a year as intern in a hospital. Those who wish to perfect themselves in any particular branch of medicine must prolong this hospital residence, often for from three to six years. The financial return throughout this training seldom rises above the subsistence level, although during their hospital residence, at least, these men are performing useful services. Under this system educational opportunities largely depend upon economic self-sufficiency. Of those who do not belong to the fortunate leisure class it is too often the unambitious who linger in our hospitals and medical schools, preferring security on a pittance to the struggle of competition. The movement to pay interns, which is rapidly gaining strength, especially in public hospitals, has justice to recommend it. If it finally prevails, however, it will place an additional burden on institutions which are already in financial straits.

It is unnecessary to linger long upon the enormous physical plant which the modern medical school must possess and maintain. The faculty, which only a generation ago was composed of physicians who derived their income from practice, must now include members who have not even had a medical

education (physicists, chemists, biologists, etc.) and who are dependent entirely upon their educational salaries. The incomes of members of the clinical faculties of the best schools are coming increasingly from salaries instead of private practice, as medicine becomes more complex and the educational responsibilities more exacting. These changes have undoubtedly improved the quality of teaching; but the scale of remuneration is so low that only those who have an extraordinary interest in investigation and teaching can remain on the full time faculty. And these have too little opportunity for the pursuit of the activities which alone can compensate the economic and social sacrifices they have made. Medical teaching has few of the allurements of academic leisure because it includes, besides the usual educational duties, responsibility for the care of patients in an exemplary manner. Since these clinical functions constitute a public service, in most instances neither hospital nor medical school feels any obligation to finance them separately.

The chief laboratories of the clinical departments of a medical school are hospitals. Without them no school can possibly survive. The old days of apprenticeship in the offices of practitioners are gone. Because teaching hospitals are indispensable to universities, the communities in which these institutions are placed adopt a mendicant attitude. The services of the schools and hospitals are accepted like the manna from heaven, while funds to support them must be sought from Foundations and philanthropically minded individuals. Although most of these institutions receive some aid, directly or indirectly, from one or more branches of the government, this rarely, if ever, even repays them for the burden they assume in behalf of the government.

The plight of hospitals which neither receive government aid nor have educational connections is even more deplorable. Unless they can find some fairy godfather to support them in luxury their facilities must be allowed to deteriorate or some of their patients must be charged fantastic amounts in behalf of the others. Services of physicians to the indigent in these hospitals either in wards or out-patient departments, are almost invariably gratuitous. Despite the highest ideals of these physicians, these services must often be relegated to a position of secondary importance in the struggle for a livelihood. In addition to providing care for its own inmates the modern hospital usually offers to the physicians of the community diagnostic and therapeutic facilities. In theory these services are manned by a more or less expert staff. In actual fact, since hospitals can not afford to remunerate this staff generously nor offer it opportunities for personal development and original work, the personnel is not usually of the highest quality. The future for its members is either to supplement their salaries by increasing private exploitation of their special training or to sink to the position of high-class technicians.

The productive investigations which advance medical knowledge are conducted chiefly in the medical schools and hospitals of this country.

Special Research Institutes and Public Health Departments of the government contribute to the total. Owing again to limited time and equipment, the part played by the private practitioner in the scientific advance of medicine becomes steadily less important. Even the organized forces of medicine contribute little but publicity. Both physicians and the public are proud of the important place which our country has attained in medical science; both benefit by these scientific achievements; but both discharge their responsibility chiefly in boasts.

Here, as I see it, is the crux of the dilemma. The great majority of physicians in this country is engaged in the distribution of medicine, not in its production. The solutions they offer for problems of health are naturally devised from the distributor's point of view. They are not uninterested in education nor unaware of the need for expansion of hospitals and educational machinery; but their proposals for the improvement of medicine are limited chiefly to measures which will allow them to utilize the resources of medical schools and hospitals for the care of their patients. They clamor for post-graduate courses by which they may be kept abreast of medical advances, from schools that are hard pressed to meet their obligations to undergraduate medical students. They ask that they be allowed as individuals to exploit hospitals and the diagnostic and therapeutic facilities that these institutions offer. They even demand the right to dispense, without control, materials provided by the government public health services. They exploit scientific discoveries to which they have contributed nothing. The burden of providing and maintaining all these services falls directly neither on them nor their patients, but is divided between government and philanthropy.

On the other side stands the consumer complaining of the unsupportable costs of medicine and searching for means to meet the bills for doctors, nurses, drugs, and possibly maintenance in a hospital. His attention is also centered on the process of distribution; his interest lies in his own illnesses. His powers of discrimination are slight; his insight into the problems of health and medicine slighter. He knows only that he wants both of the highest grade at the lowest possible price. He must be taught with stern honesty what these desires entail, not placated with fairy stories about the happy state of the present system of medicine.

Evidently, if reorganization for the improvement of medical care is contemplated, production must be considered quite as much as distribution and consumption, because it is production that ultimately determines the quantity and quality of the supply. It is in their complete neglect of the productive aspects of medicine that such measures as health insurance and ordinary coöperative organizations fail to meet the situation. It is in the same respect that the untrammelled control of medicine by its distributors falls short. In every other walk of life part of the payment which the distributor receives from the consumer for services reverts to the producer. It would be unfortunate if medicine followed this general commercial prac-

tice. But, if it does not, it must ultimately find an alternative, and the only sound alternative thus far discovered for the support of non-remunerative enterprises is governmental subsidy.

It is my impression that the government alone can assume the burden of providing, maintaining and correlating the necessary medical resources. Such a suggestion immediately arouses cries of bureaucracy, and corruption, as if these were inevitable attributes of our political system. The medical profession should be the first to deny such allegations. It is its proud boast that the public health services of this country have been free from corruption and politics. But, in any case, there is no good reason to believe that government direction would be worse than the whims and vagaries of philanthropists or the publicists and promoters who have the disposition of large funded fortunes. Nor are the subsidies from the manufacturers of proprietary foods, drugs and medical instruments likely to direct education, investigation and practice into the most desirable channels.

It is my opinion, further, that costs must eventually be collected by general taxation. Those who can pay for their own care and prefer to patronize physicians of their own choice should not escape the general tax on this account; because this will not be imposed merely to pay for personal services but for the productive work that makes those services valuable. It is rather amusing to reflect that at the present time most of the advances in medicine which the rich enjoy are developed in hospitals and institutions through the instrumentality of indigent patients. The fees which the rich pay, however, do not return to the support of these institutions or the patients in most instances, but go to the practitioner who is exploiting the new medical discoveries. The discharge of his deeper medical debt should not be left to the caprice of the wealthy patient, because there is no assurance that his whim will be wisely directed. It is much more likely to be dictated by emotions connected with his personal experiences than by the general medical interests of the public.

Preconceptions and prejudices must be abandoned, whether they be political, economic, social or medical. There are those who shudder at the thought of governmental control in any province of life, others to whom the word federal has a peculiarly vicious significance. Yet all recognize that due participation of local, county, state and federal governments in the interests of the common weal is a necessary bulwark against anarchy. All these branches of the government at present share the burden of public medical and health services; no one of them can or should be completely excluded. The most pressing present problem of government is the discovery of the formula that will assure proper allocation of responsibility and expert control. This is more likely to be attained, in my opinion, if the initiative is taken by those who are expertly trained. In any reorganization of medicine this means primarily physicians. In attacking the problem, the improvement of medical care, not costs nor remuneration, must be the prime

objective. No one yet knows what the highest quality of medical care would cost nor what it might be worth.

These are bold statements and are sure to arouse at once cries of socialism or worse. I should hope this company would not be frightened by mere words. Large ends can not be gained by little means and the goal I have set is highly ideal. A sweeping program suddenly imposed on this country as a whole, out of the head of any Jove, would undoubtedly create confusion, if not chaos. Thoughtful investigation and experiment promise more than grandiose projects born of emotional preconceptions. The program must be built in an evolutionary manner, step by step, with thought to the resources and personnel now available and the need for developing more and better resources and personnel. The investigation of the extent of medical indigence projected by the American Medical Association must be searching and not too limited in its scope. But this should be only the first of a series of investigations which must measure the extent of our assets as well as our liabilities. Experimentation in the solution of local and general problems of medical care must be encouraged, not suppressed. Education and investigation must be supported and extended and opportunities for work in these fields must be multiplied and made more attractive, with every protection against inexpert control, regimentation and the destruction of initiative and imagination. Until these investigations have been made anyone is arrogant indeed who claims that he has a program that will solve the problems of medicine in a "nation comprised of forty-eight states in which climatic, economic and social conditions vary greatly." But he who doggedly resists change either because of personal satisfaction with his present condition or because Utopia seems an idle dream, betrays both the art and the science of medicine. Because both art and science know no limits and defy all restrictions.

CASE REPORTS

GASTROSCOPIC OBSERVATIONS OF SYPHILIS OF THE STOMACH *

By J. B. Carey, M.D., F.A.C.P., and R. S. Ylvisaker, M.D., F.A.C.P.,
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English medical literature contains no gastroscopic description of syphilis of the stomach of the *linitis plastica* or leather bottle type. Schindler's [1] English text mentions cases seen with Moutier and referred to in the latter's French text, and in addition describes two syphilitic stomachs of contracted hour-glass type, both of which had been treated (one operated upon) and which showed only healed scars at time of gastroscopy. Renshaw,[2] in discussing the differential diagnosis of tumors of the stomach, refers to syphilis of the stomach as having "no constant characteristics." "There have been tumors with and without ulcers. The positive blood serum reaction is the only definite differential point." Kerkhof [3] describes a case of a large ulcerous lesion thought to be luetic because of a positive Kahn reaction, but which was subjected to biopsy because of the suggestive appearance of malignancy. The biopsy showed definite perivascular infiltration and lymphocytes and plasma cells deep in the submucosa, and the suspicion of syphilis was confirmed. He noted gastroscopically subsequent healing to scar tissue after antiluetic treatment. Henning's [4] English text does not mention syphilis of the stomach specifically. Swalm, Jackson and Morrison,[5] in a report of different types of chronic gastritis, include one case marked "luetic etiology," but no clinical details or reports on serologic examination are given.

Gutzeit and Teitge [6] show two pictures of syphilis of the stomach. One (*Bild 56*) is described as a red, speckled, rough mucosa with thick swollen folds in a male patient 56 years of age, with achylia and "latent lues." Another, a patient with tabes dorsalis (*Bild 71*) also shows a red-flecked mucosa with hypertrophic changes and swelling of folds. Both of these pictures resemble the appearance seen in our case after treatment. They further state that cases of lues with primary lesions and with skin eruption show nothing gastroscopically or only a mild superficial catarrh. The treated or healed syphilitic patients showed superficial catarrh with atrophic changes, sometimes atrophic gastritis, rarely hypertrophic gastritis, more often a swollen condition of the mucosa. In latent lues a smooth condition of the mucosa was seen, regardless of whether the patient had or had not received treatment, and in tabes a similar condition, with hypertonicity (or contracture?). Their conclusion is that the tendency in syphilis, where any change in gastric mucosa occurs, is toward an atrophic state.

Moutier has the most complete gastroscopic description of syphilis of the

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stomach. He divides the cases into those showing tumor (gumma) formation and leaving a localized scar on healing; ulcerative forms, single or multiple, also on healing leaving scars, with more contracture and distortion of the stomach (hour-glass); and those showing a generalized gastritis, often hemorrhagic, resulting in atresia (*linitis*) by submucosal involvement. The plates shown in his text (XII, 1 and 2, and XII, 3) illustrate the localized varieties.

The only cases of *linitis plastica* comparable to our own are described by Moutier [7] (page 167):

> The first is that of a 60-year old man, known to have been luetic for 25 years, with achylia but, at the time of observation, with a negative Wassermann. The roentgen-ray examination showed a small, contracted stomach transversely situated high under the diaphragm and liver, with a small air bubble and normal emptying time. Gastroscopy showed a very small gastric lumen, hardly distensible by inflation and extremely intolerant to air. Hypersecretion with adherent mucus on the walls was noted. During the examination there was very violent antral spasm. The pylorus was hardly visible, high and to the right (posteriorly placed). The folds were very large (thickened) in the antrum. There were several hemorrhagic areas on the lesser curvature. The mucosa of the body of the stomach appeared thick, but not hypertrophic.
>
> Another case was of a 40-year old man, said to be luetic, untreated but with negative Wassermann (?) and achylia. The roentgen-ray examination showed an extremely contracted antrum. Gastroscopy in this patient showed all normal folds and markings effaced and the surface of the mucosa granular, superficially ulcerated in places and hemorrhagic in other areas. After anti-luetic treatment the roentgen-ray appearance of the stomach was restored to normal, but a second gastroscopy was not done.
>
> A third case was of a 45-year old man, said to be luetic, in whom the gastroscopic appearance was practically the same, except that the antrum could not be visualized at all (because of contracture) and there was more atrophy of the mucosa. This case also showed improvement after anti-luetic treatment on roentgen-ray observation, but another gastroscopy was not done.

Moutier [8, 9] has more recently discussed pseudo-cancer of the stomach. He describes in detail six cases which appear to be carcinoma by roentgen examination but because of the history of the patient and the appearance gastroscopically, together with the response to antiluetic treatment, were finally diagnosed as forms of syphilis of the stomach. He divides these cases into the syndrome with tumor and no emaciation, dyspeptic syndrome with pronounced emaciation and the hemorrhagic syndrome.

In addition to the case to be reported, one of us (J. B. C.) has examined gastroscopically three other patients with known syphilis (one with cirrhosis of the liver). In two of these an atrophic mucosa was seen, indistinguishable from gastritis of other etiology. The third showed hypertrophic mucosal changes.

Case Report

The patient is a white married male (J. W.), aged 64, caretaker for the barns of a creamery company. He first reported for examination at the Out-Patient Department of the University Hospital September 29, 1937.

His presenting complaints at that time were: (1) burning and shooting pains in both lower extremities; (2) weight loss; and (3) insomnia. The pains in the ex-

tremities had been noticed first in the left foot about one and one-half years previously and had not extended to both legs until six weeks before examination, following a long automobile trip. He knew that he had gradually lost weight during the preceding year but did not know exactly how much. He had not been able to sleep well for three or four weeks. There had been no gastrointestinal symptoms except slight rectal bleeding on a few occasions, and more recently a transient attack of "gas pains." Slight dizziness had been present off and on throughout his present illness.

He had had scarlet fever at the age of 18, and fractured a bone in the right foot at the age of nineteen. Suppurating infections of the right hand had occurred twice. All teeth had been removed at the age of sixty-two. He denied knowledge of any venereal infection. He had never drunk alcoholic beverages and smoked and chewed tobacco moderately.

He was unable to give any account of his family history.

The patient was a well-developed tall white male in a fairly good state of nutrition. The abnormal findings were: (1) Unequal, irregular pupils which failed to react to light; (2) a smooth tongue with a leukoplakial patch; (3) an accentuated second aortic sound with a systolic and diastolic murmur heard at the second left intercostal space, but no evidence of congestive failure; (4) large external and internal hemorrhoids; (5) moderate varicosities in both lower extremities. The pulse rate was 96, the blood pressure 110 systolic, 72 diastolic.

The following were the significant laboratory data: The urinalysis was normal. The blood hemoglobin was 51 per cent, red cell count 4,400,000, white cell count 6,600 with a normal differential count. The red cells show hypochromasia, anisocytosis and poikilocytosis. The blood Kolmer, Kline and Kahn reactions were strongly positive. Analysis of gastric secretions showed 14° free acid and 34° total acid after histamine. There was also acid response after an alcohol test meal, but on several occasions no free hydrochloric acid was found in the fasting contents. There was a small amount of blood in the stool by chemical test. The fasting blood sugar content was 152 mg. per 100 c.c. Spinal puncture brought out a clear fluid under a pressure of 8 mm. mercury. The cell count was 1 mononuclear per centimeter, Nonne and Pandy tests were positive, Kolmer negative, Kline 2 plus. Sugar was present in the amount of 95 mg. per 100 c.c. Specific precipitation developed in colloidal gold solutions. The culture was sterile and a direct smear revealed no organisms.

Roentgen-ray examination of the gastrointestinal tract was reported as follows by the roentgenologist:

October 5, 1937: "Colon: Normal except for a few diverticula of the sigmoid colon."

October 22, 1937: "Stomach: The esophagus is normal. The barium fills the stomach and pours rapidly out, filling the cap, which is large and flaccid, and empties rapidly into the small bowel. The lower two-thirds of the stomach is diffusely narrowed and rather rigid, but shows minimal peristaltic waves. The mucosa of this region also appears somewhat abnormal. The fundal end of the stomach is elastic and dilates normally. The findings are strongly suggestive of lues of the stomach or possibly a diffuse infiltration of the stomach wall by scirrhus carcinoma (figure 1).

"Conclusion—*Linitis plastica.*"

There was a dilatation of the ascending aorta seen by orthodiascopic examination. The heart measurements were 7.7 cm. to the left and 4.0 cm. to the right of the midline, with a total transverse thoracic measurement of 27.6 cm.

A left axis deviation but no other abnormality was observed in the electrocardiogram.

The first gastroscopic examination was done on October 27, 1937, the details of which are reported below. Beginning on November 20, 1937, 18 intramuscular injections of bismuth salicylate in oil were given at weekly intervals until April 6,

1938. The patient received no treatment from April 6 to April 20, but had four bismuth injections from April 20 to May 11 and none thereafter until May 25, 1938. He was also given potassium iodide in doses of 10 drops of the saturated solution three times daily for a period of one month starting November 19, 1937. In addition to his anti-luetic therapy he was given iron in the form of ferrous sulphate orally. By May 25, 1938, the hemoglobin had risen to 78 per cent and the red blood cells to 4,400,000.

On this regime his general condition improved progressively, and he continued to be free from gastrointestinal complaints. The second gastroscopic examination was carried out April 14, 1938 (noted in detail subsequently). Stool examination on April 18 showed no occult blood. It had been intended that the stomach be re-

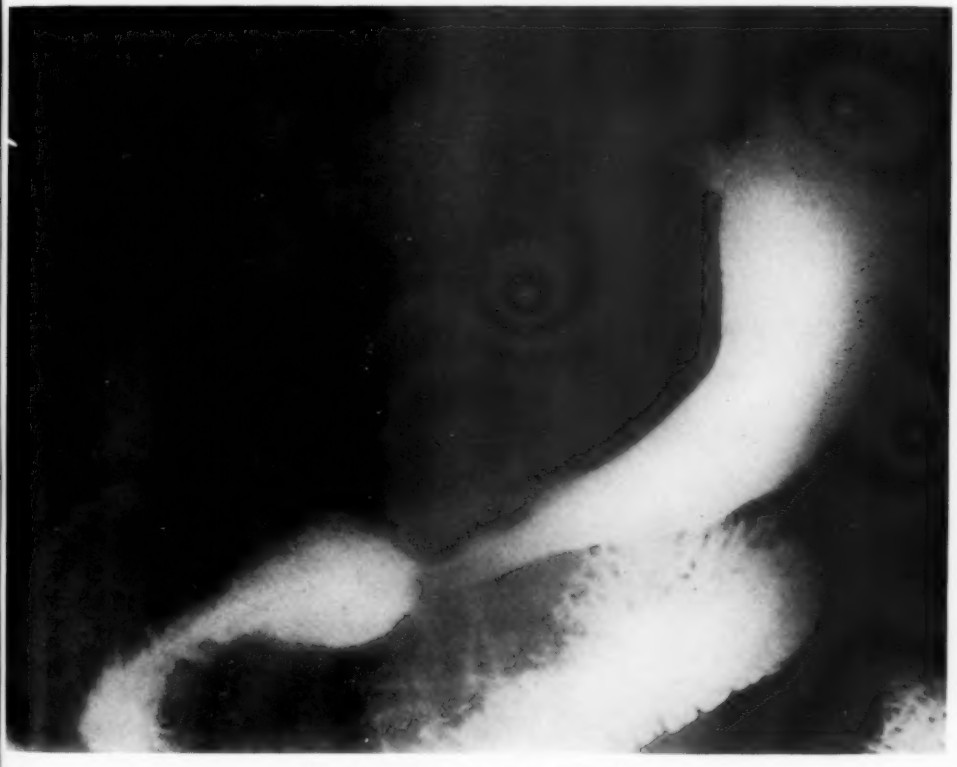

FIG. 1. Syphilis of the stomach.

examined roentgenologically at that time, but through misunderstanding and later because of an accident to the patient this was not done.

Roentgen-ray examination of the stomach was, however, done on June 1, 1938. The report of that examination as given by the roentgenologist is as follows: "The same findings in the stomach now that were previously reported; although the walls appear somewhat more flexible, no real peristaltic waves could be demonstrated. There is a very small out-pouching of the anterior wall which may be a small crater or simply a peculiar mucosal arrangement. Findings at this time indicate some improvement of the process since the previous examination, which lends support to the diagnosis of *linitis plastica* on a luetic basis." (Figure 2.)

The first gastroscopic examination (October 27, 1937) was easily carried out, with the 50° gastroscope. The lumen of the stomach was seen to be contracted.

Very little air could be introduced and the walls of the stomach were at all times close to the objective. The normal anatomical landmarks such as the cardiac shelf, fundus pouch, *angulus* and *musculo-sphincter antri* were not present. All normal folds and rugations were effaced and instead broad, thick folds and indentations were seen. The mucosa was smooth and pale (anemic—hemoglobin at this time 51 per cent). The walls appeared as though stiff and infiltrated. No blood vessels were seen. The region of the antrum was seen as an oval tubular channel, funnelling down to the pylorus. The pyloric opening was of irregular shape, tending to be slit-like and appearing to be partly open. There were no waves going down the antrum as usual, but rather a total bellows-like closing movement of the entire antrum. The pylorus would occasionally contract, not apparently in response to the antral move-

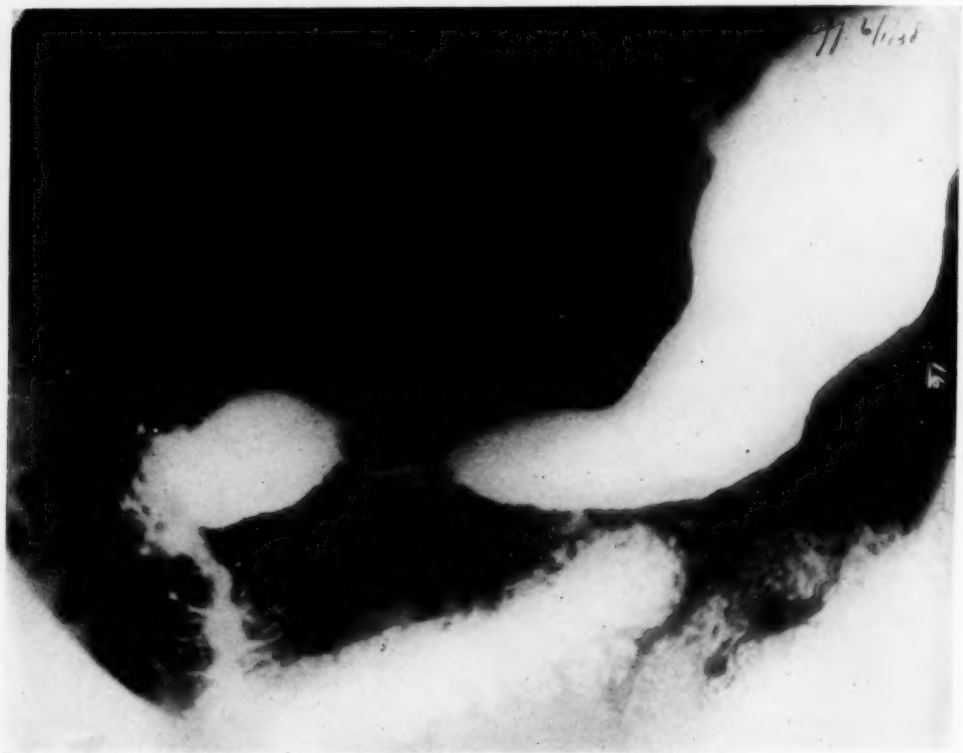

FIG. 2. Syphilis of the stomach—after treatment.

ments, but spasmodically, irregularly and incompletely. There were no hemorrhagic spots or ulcerations seen. The impression was that of a stiff, almost tubular structure lined with a sort of smooth pink frosting or meringue, irregularly creased and indented like an old mattress. (Figure 3.)

The second gastroscopic observation was made on April 13, 1938. In the interval between these two examinations the patient received iodide and bismuth therapy as noted in the case report. At this time normal anatomical features could be distinguished, that is, the *angulus*, the *musculo-sphincter antri*, the cardiac shelf and the fundus pouch. There were waves going down the antrum from the region of the *angulus* as is normally seen, and the pylorus opened and closed synchronously with these waves. There were the usual coarse folds and rugae of the greater curva-

ture and posterior wall. The mucosa was of normal color (hemoglobin was 69 per cent January 14), although it appeared somewhat thicker and smoother than usual.

A third gastroscopy was done May 25, 1938. As noted in the case report, there had been a cessation of therapy because of an accident to the patient and his consequent absence from the Dispensary. At this time the antrum was seen to be con-

FIG. 3. Gastroscopic appearance of syphilis of the stomach—before treatment.

FIG. 4. Gastroscopic appearance of syphilis of the stomach—after treatment.

tracted, tubular and with the pylorus appearing small, far away and somewhat stiff. The *musculo-sphincter antri* could not be identified and the angulus structure was reduced to a ring-like opening with the rim stiff and thick. The color of the mucosa was normal (hemoglobin now 78 per cent). The contractions of the antrum were irregular and the pylorus never seemed to close completely. The mucosa seemed thick and, on the posterior wall and floor of the antrum, was irregularly nodular. The

body of the stomach had also a thickened mucosa, creased in some areas, and in other places of a pavement or cobbled appearance. Near the cardia the mucosa seemed atrophic, although no blood vessels were seen. There were a few hemorrhagic spots near the cardia. Our impression was that there had been a recession toward the original appearance; that is to say, the general appearance was not as nearly normal as in second examination, but not as abnormal as when first seen. (Figure 4.)

Conclusion

In conclusion, then, we have described the condition of the stomach as seen gastroscopically in a 64-year old syphilitic man without gastric symptoms, responding favorably to bismuth and iodide therapy, and tending to regress during a period when treatment was unavoidably discontinued. The roentgenological appearance of this stomach corresponded with what has been generally called the *linitis plastica* or leather bottle type of deformity. Gastroscopically the stomach was found to be contracted, with stiff walls, smooth mucosa and obliteration of anatomical landmarks. This appearance seemed to have been partially restored to that of a normal stomach under treatment.

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COARCTATION OF THE AORTA; REPORT OF A CASE WITH ASSOCIATED ANOMALIES *

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Coarctation of the aorta is a very interesting congenital anomaly in which there is a narrowing or complete obliteration of the aorta in the region of the insertion of the *ductus arteriosus,* distal to the origin of subclavian artery. Bonnet [1] has divided this anomaly into the infantile and adult types. The infantile type consists of a diffuse narrowing of the aorta between the origin of the subclavian artery and the insertion of the *ductus Botalli.* The adult type is characterized by an abrupt constriction of the aorta a little beyond the subclavian artery, as if the aorta had been narrowed by a ligature.

* Presented at the Annual Session of the American College of Physicians, Bellevue Hospital Clinic, New York City, April 8, 1938.
From the Fourth Medical Division, Bellevue Hospital, Dr. Charles H. Nammack, Director.

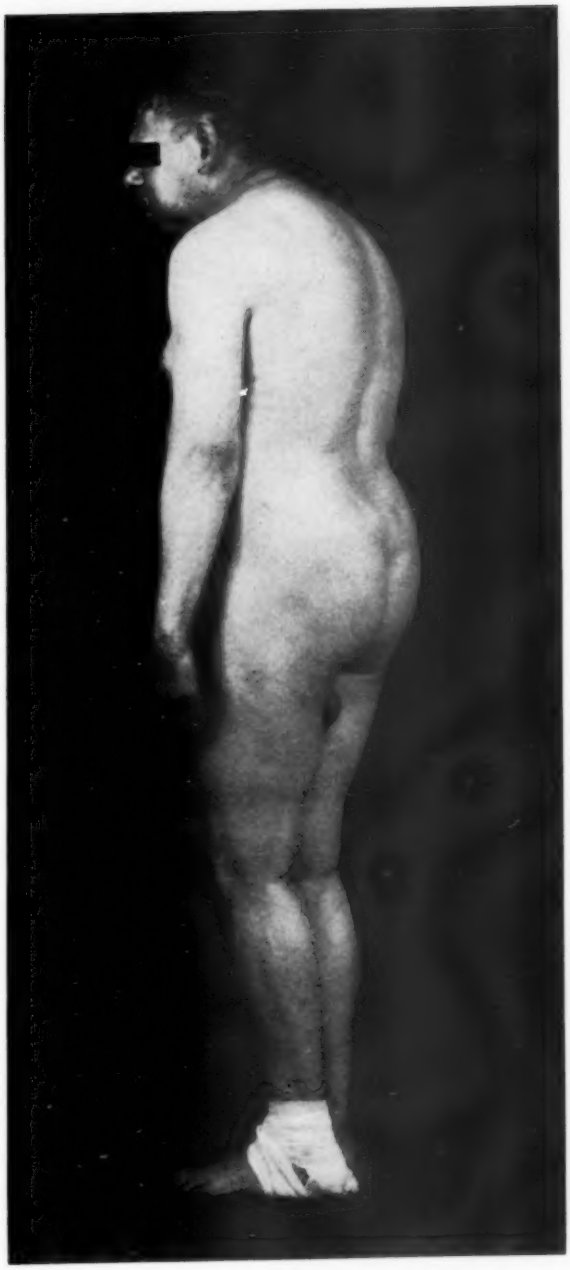

FIG. 1. Well nourished patient, with microcephalus.

In this paper no attempt will be made to review the literature, as this has been admirably done by Abbott [2] and by others.[3] Likewise, the etiology and pathogenesis of this anomaly have been adequately discussed by these authors, and will not be considered here. In presenting our case of coarctation of the aorta we wish to draw attention to the importance of associated anomalies and to stress certain diagnostic features of this remarkable condition.

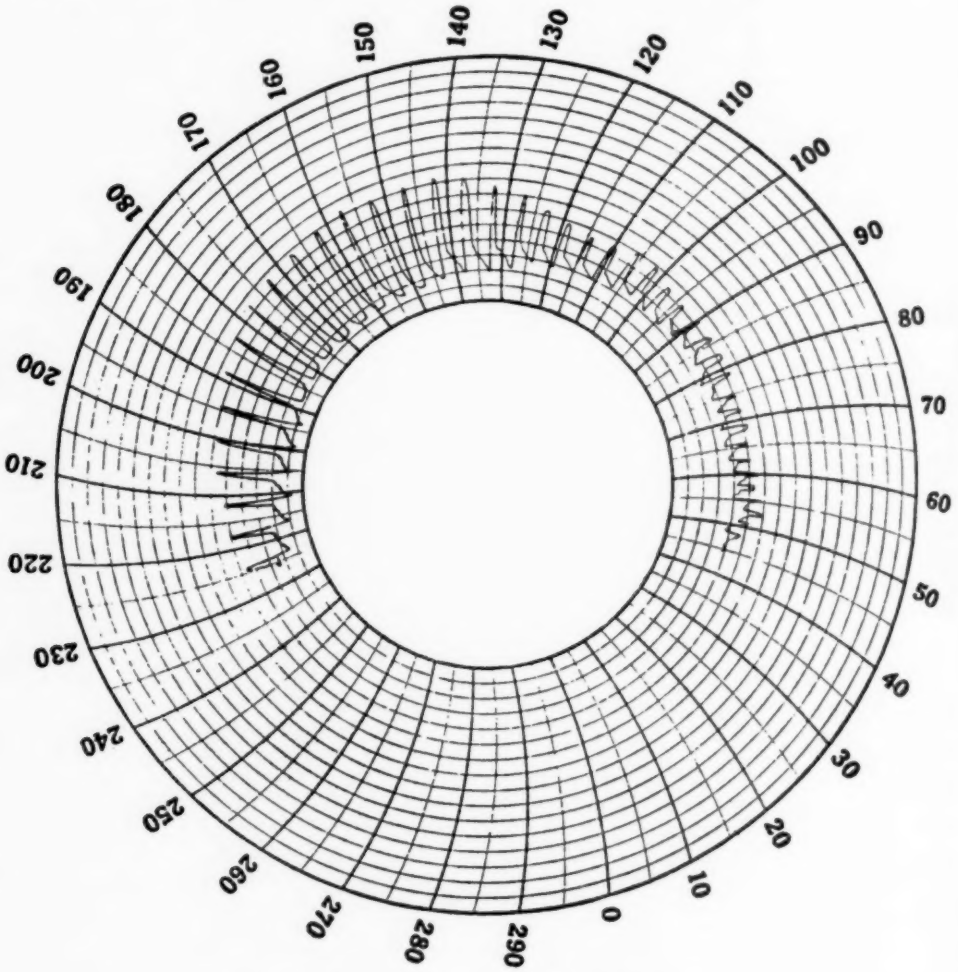

FIG. 2. Oscillometric tracing of right forearm.

CASE REPORT

B. E., a man aged 38, entered Bellevue Hospital, March 9, 1937, complaining of pain in the left side of his chest of five hours' duration. The pain did not radiate but was associated with dyspnea. He had had several similar attacks during the preceding three months. His past history revealed that he had been a backward child and later had been an inmate in a psychopathic institution for several years. He had had some difficulty in walking as far back as he could remember.

On examination the patient appeared well nourished and plethoric. His head was of the microcephalic type (figure 1). There was definite mental impairment. There was wide separation of his teeth. The lips were moderately cyanosed. The pupils reacted to light and accommodation. The chest was barrel-shaped with an increase in the antero-posterior diameter, and there was a moderate kyphosis of the dorsal spine. The lungs were clear. The heart was moderately enlarged to the left

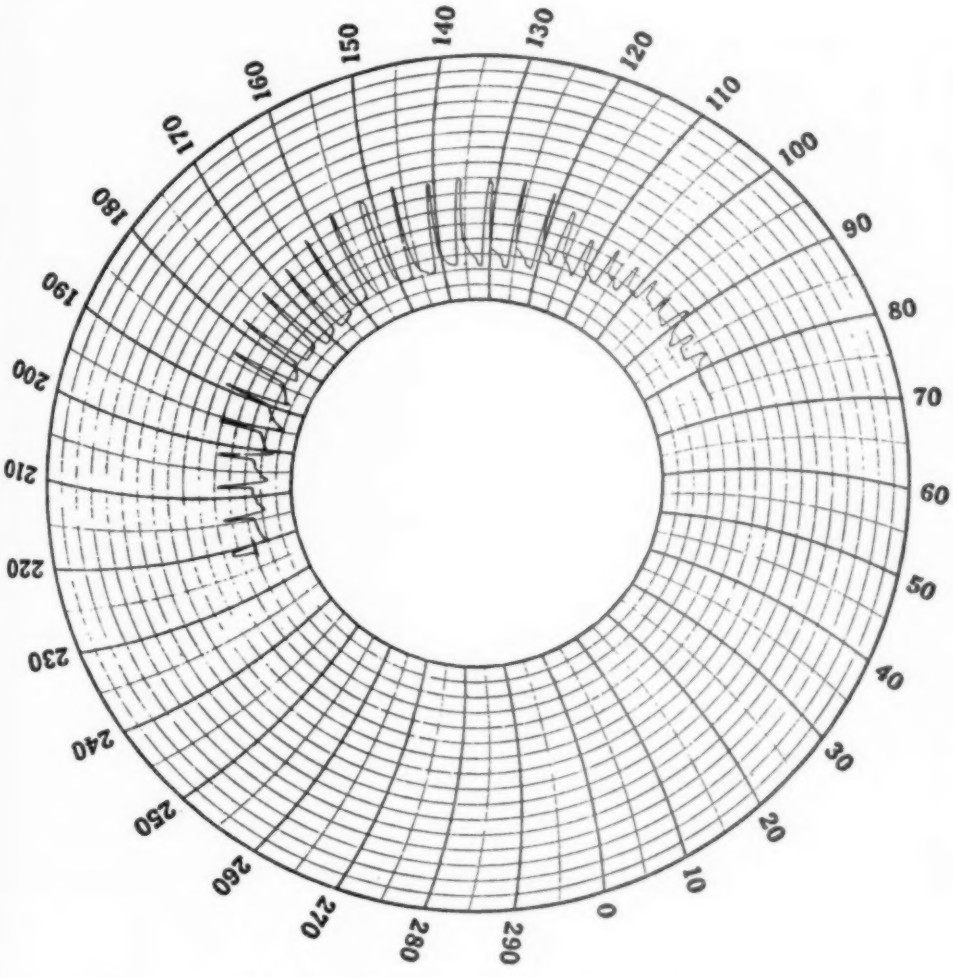

FIG. 3. Oscillometric tracing of left forearm.

and right. The first sound at the apex was split and followed by a harsh systolic murmur. A short systolic murmur was heard also at the base of the heart. The pulmonic second sound was greater than the aortic. The blood pressure was 180 systolic and 130 diastolic in his right arm and 204 systolic and 114 diastolic in his left arm. The abdomen was enlarged but showed no masses or fluid. The liver and spleen were not felt. The extremities appeared well proportioned in relation to his trunk. There was a small hemangioma over the outer aspect of his right heel. The femoral pulsation was feeble on both sides. There was a bilateral positive Chaddock

and a Babinski on the left side. There was no clonus. The abdominal reflexes were absent. There were no sensory disturbances. He had no ataxia, but had a waddling gait, with a tendency to drag the left foot. These neurological signs were strongly suggestive of bilateral pyramidal tract involvement, particularly on the left side. The evidence of developmental defects in a comparatively young adult with hypertension suggested to us the diagnosis of coarctation of the aorta.

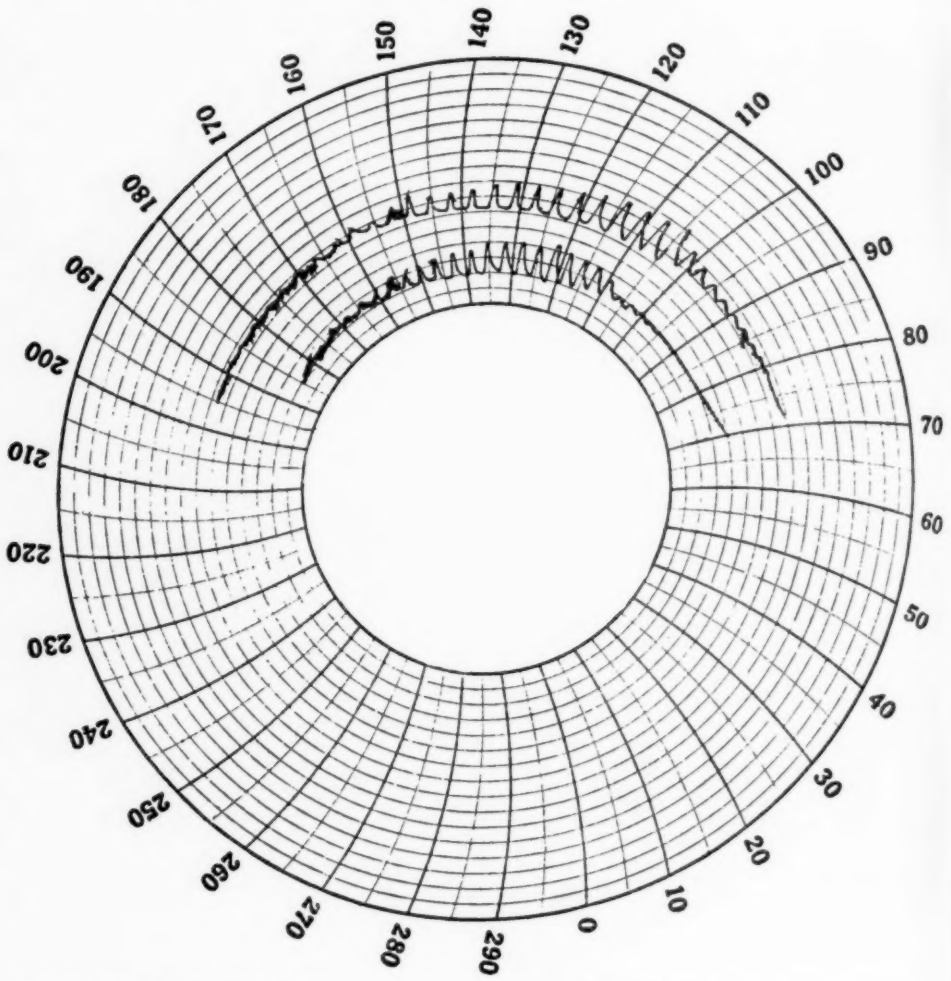

FIG. 4. The upper curve is oscillometric tracing of right leg and the lower curve represents the left leg.

A closer study of the patient was then made, and this revealed the presence of the characteristic physical signs of this congenital anomaly. There was marked pulsation with a harsh systolic murmur in the upper part of the interscapular region along the dorsal scapular vessels. A similar murmur was heard also over the carotid, upper intercostal, internal mammary and deep epigastric arteries. The radial pulses were full and sustained, while femoral pulsations were barely perceptible. There was marked hypertension in the upper extremities, while the blood pressure in the

lower extremities could not be elicited. The fundi showed increased tortuosity and pulsation of the retinal arteries.

Oscillometric readings revealed forceful pulsation in the arms and curves of diminished amplitude in the legs. Fluoroscopy and roentgenography showed moderate enlargement of both right and left ventricles, absent aortic knob, marked prominence of the pulmonic conus and indentation on the under surfaces of many of the ribs (figure 5). In the left oblique view the aortic arch and the descending aorta could not be visualized (figure 6). The electrocardiogram showed left axis

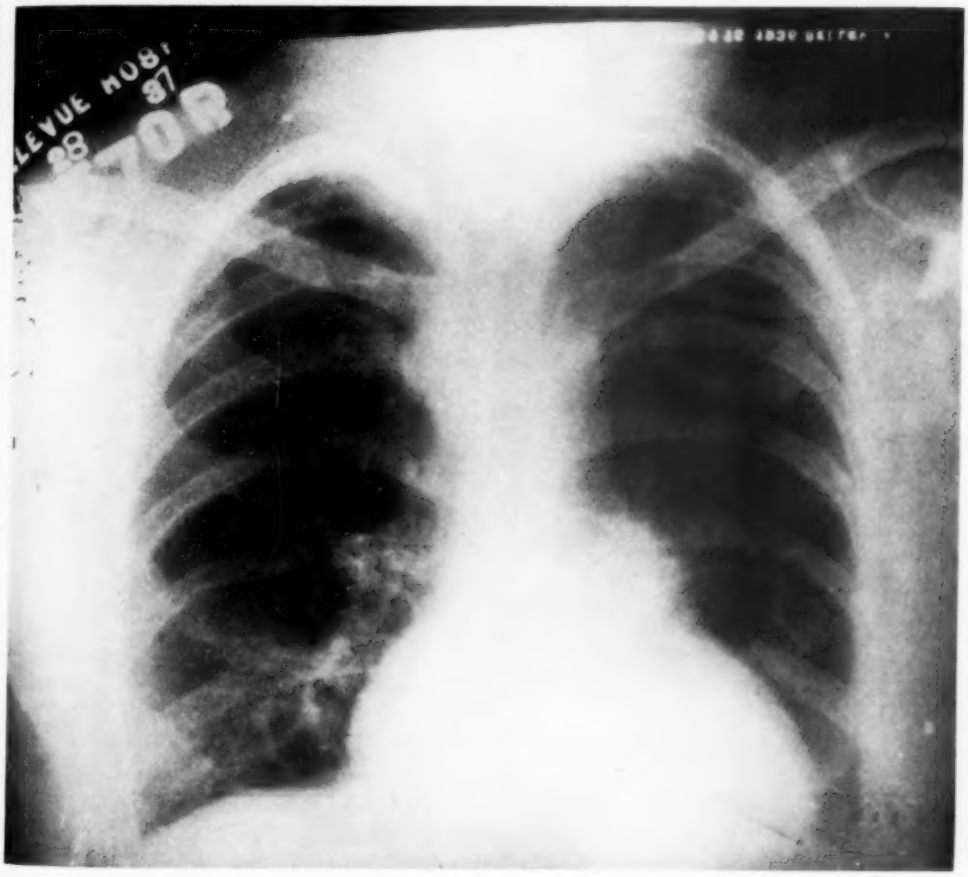

FIG. 5. Antero-posterior roentgenogram of chest. Note absence of the aortic knob, prominent pulmonic conus and indentations of ribs.

deviation and deep Q-waves in Lead III. The blood count showed 4,790,000 red blood cells with 98 per cent hemoglobin and 10,200 white blood cells with 75 per cent polymorphonuclears and 25 per cent lymphocytes. The blood Wassermann was negative. The decholin circulation time was 13 seconds and ether time 6 seconds. The venous pressure was 7 cm. of water. Urinalysis was negative, but a concentration test showed some impairment of function. The phenolsulphonephthalein excretion was 60 per cent in two hours. The blood chemical tests showed a non-protein nitrogen of 34 mg. per cent and a sugar of 106 mg. per cent. Intravenous pyelograms showed the kidneys to be of normal size and contour.

With rest in bed the patient improved and was discharged at his own request on March 19, 1937.

He was re-admitted to the hospital on April 26, 1937, complaining of paroxysmal nocturnal dyspnea and of attacks of precordial pain, with radiation to the arms. The physical findings were essentially the same as those previously described. The electrocardiogram, however, showed evidence of active myocardial changes. The T-wave in Lead I was inverted and preceded by a convex shoulder. In Lead II the T-wave was diphasic and the R–T segment was convex. There were frequent premature contractions of ventricular origin. He was discharged as improved on May 6, 1937, and was subsequently observed in the Out-Patient Department.

Comment

This case presents a number of very interesting and important points. As previously stated, the diagnosis of coarctation of the aorta was first suspected because of the presence of external developmental defects. The presence of associated anomalies either in the heart itself or in other parts of the body has been emphasized by a number of writers on the subject. As pointed out by Abbott [2] the presence of such anomalies forms an interesting link in the chain of evidence pointing to developmental arrest as the chief causative factor. To the best of our knowledge, this is the first case on record in which microcephalus with impaired mentality and hemangioma of the skin were associated congenital defects. Bronson and Sutherland,[4] however, reported a case with slight mongolianism. The presence of mental impairment is a matter of particular interest, since these subjects usually show normal, and not infrequently above average, intelligence.

The presence of associated anomalies in the cardio-vascular system has been a subject of particular interest. As pointed out first by Bonnet [1] and later by Abbott,[2] major or more complex anomalies are more commonly combined with the infantile type, while the minor anomalies are more frequently found in the adult form. The outstanding major anomalies are biloculate or triloculate heart, transposition of the arterial trunks and pulmonary atresia. The more important of the minor anomalies include bicuspid aortic valve, anomalous origin of the arteries from the arch, persistent left superior vena cava, defects of the aortic septum, subaortic stenosis and cerebral aneurysms.

The enlargement of the right ventricle in our patient, and particularly the marked accentuation of the pulmonic conus suggested the presence of another cardiac anomaly. One can only speculate as to the nature of this possible additional lesion, since the patient presented no clinical signs of patent ductus, pulmonary stenosis or of other valvular or septal defects. The presence of a patent ductus arteriosus seemed to us the most likely possibility. Failure to visualize the aortic arch and descending aorta in the left oblique roentgenogram suggested also the presence of aplasia of the aorta. A similar case, with patent ductus and aortic aplasia was reported by Ulrich.[5]

Enlargement of the left ventricle is, of course, common in adult coarctation and may be due either to the hypertension or to the presence of valvular lesions produced by intercurrent infections. It is to be noted, however, that cardiac hypertrophy is not an essential feature of even the most extreme degrees of coarctation in subjects living to an advanced age.

It is difficult, if not impossible, to establish with certainty the basis of the patient's neurological signs, which were suggestive of bilateral pyramidal tract in-

volvement. We have already referred to the not infrequent presence of cerebral aneurysms as an associated anomaly in cases of coarctation of the aorta. These aneurysms may suddenly rupture and cause a spontaneous meningeal or cerebral

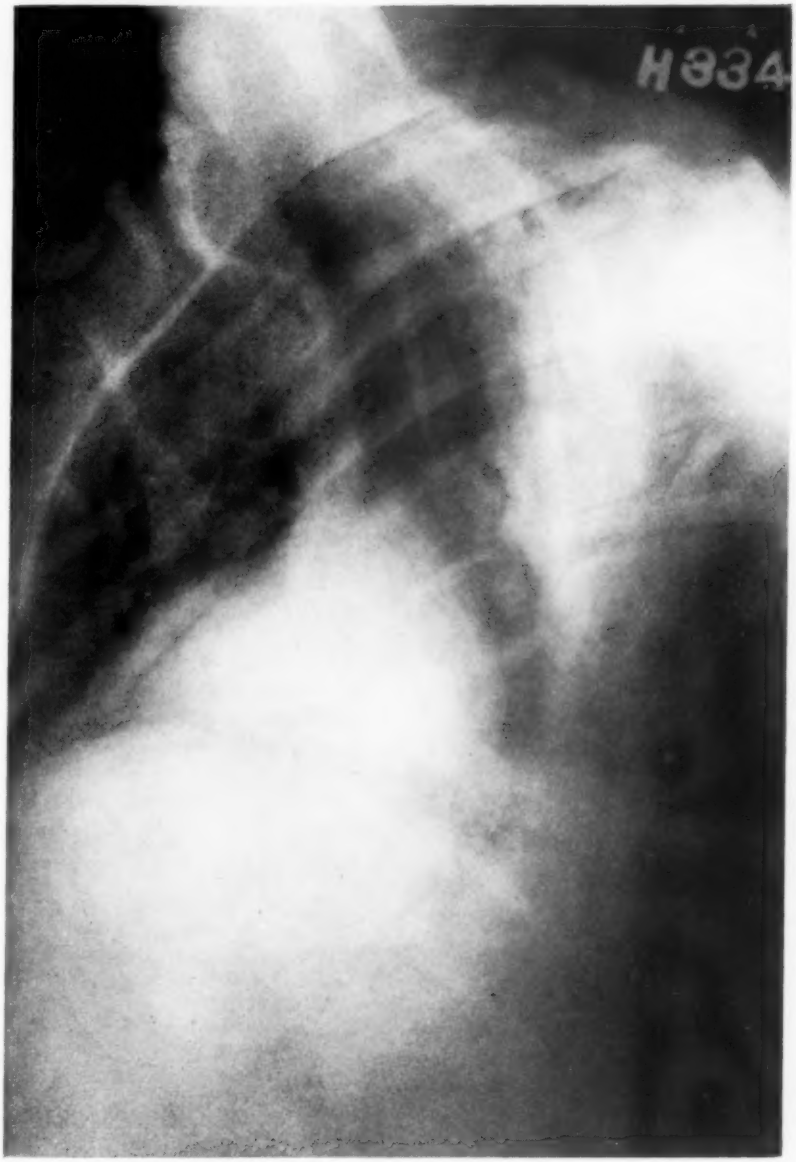

FIG. 6. Roentgenogram of heart in the left oblique view. The aortic arch and descending aorta cannot be visualized.

hemorrhage, often leading to death. In certain instances, there may be an intermittent leakage of a cerebral aneurysm, produced by the closure of a small slit-like aperture after a certain amount of bleeding has occurred, followed later

by its reopening. These patients may present alternating episodes of disturbed cerebral function and periods of relatively good health, or repeated apoplectic attacks. The phenomenon of intermittent leakage has been emphasized by several workers, notably by Parker,[6] Lichtenberg and Gallagher [7] and by Baker and Sheldon.[8] It is quite possible that our patient has had episodes of intermittent leakage, although there is nothing in the history to support this assumption. One must also bear in mind the possibility that the abnormal neurological signs were due to some congenital cerebral defect associated with the microcephalus.

With regard to the history, it is to be noted that our patient's only complaints were precordial pain and dyspnea. In the great majority of cases the patients are robust young adults who have led an active life and first consult a physician when they develop symptoms of hypertensive cardiopathy. Occasionally the condition is first discovered when the patient has a cerebral hemorrhage. Rarely intermittent claudication is the presenting complaint. It is evident that coarctation of the aorta presents no distinctive symptomatology.

The physical signs of coarctation are, however, pathognomonic, and are based on the evidences of collateral circulation above the aortic constriction with diminished femoral pulsation below it. These characteristic signs may be summarized as follows:

1. A normal or bounding pulse is noted in the vessels of the neck and upper extremities, and an absence or marked diminution of pulsation, in the arteries of the lower extremities.

2. A palpable pulsation is absent in the abdominal aorta whereas a forceful systolic thrust is present in the suprasternal notch and vessels of the neck.

3. There is hypertension in the brachial arteries and a much lower or absent blood pressure in the popliteal arteries. This is a reversal of the normal state.

4. There is evidence of a well-developed collateral circulation. Large, tortuous anastomosing arteries may be seen and palpated in the interscapular, suprascapular, axillary, and precordial regions. The internal mammary and deep epigastric arteries may be dilated and palpable. A harsh blowing systolic murmur is usually heard over these collateral vessels. A thrill frequently accompanies the murmur. The features of the collateral circulation are discussed in great detail in Abbott's [2] comprehensive and excellent article, and need not be considered here.

5. A murmur is usually heard over the aortic area, with its maximum intensity along the left border of the sternum. This murmur is frequently modified by associated cardiac anomalies or acquired valvular lesions.

While the diagnosis of coarctation can be made on clinical grounds, the use of laboratory methods is confirmatory and frequently helpful. The difference in the oscillometric curves of the upper and lower extremities is quite striking (figures 2, 3 and 4). There are also certain characteristic roentgenologic signs (figures 5 and 6). These are as follows: (1) bilateral erosion of the inferior borders of the ribs; (2) absence of the prominent aortic knob, usually associated with hypertension; (3) narrowing of, indentation, or a gap in the descending portion of the aortic arch, which is best seen in the left anterior oblique view. Not infrequently there is also dilatation of the ascending aorta. In this con-

nection it may be noted that the electrocardiogram shows, as a rule, no striking or characteristic changes.

It is evident that coarctation is not difficult to diagnose, and yet it is frequently overlooked. From Blackford's [3] statistics it would seem that this condition is probably more common than is generally supposed. The possibility of coarctation should, therefore, be borne in mind when there is evidence of hypertension or hypertensive cardiopathy in a young adult without renal disease. It is important to recognize this anomaly early in order to protect these young adults from undue physical exertion.

Summary

We are presenting a case of coarctation of the aorta associated with other congenital defects. Certain significant features of the associated anomalies are discussed. The cardinal physical signs of coarctation and the important laboratory findings are summarized. The importance of early diagnosis is stressed.

The authors wish to express their thanks to Dr. Gertrude H. B. Nicolson for valuable suggestions and criticisms.

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8. Baker, T. W., and Sheldon, W. D.: Coarctation of the aorta with intermittent leakage of a congenital cerebral aneurysm, Am. Jr. Med. Sci., 1936, cxci, 626.

EDITORIAL

RECENT DEVELOPMENTS IN USE AND ADMINISTRATION OF OXYGEN IN AVIATION AND THERAPEUTICS

Modern oxygen therapy can be said to have originated in the World War, through the demonstration by Haldane [1] of its great value in the treatment of soldiers who had been gassed with pulmonary irritants. His method of administration was by means of a mask but unfortunately the exigencies of war time prevented the perfection of details and the apparatus was neither comfortable nor economically efficient. Following the war, Stadie,[2-4] Binger [5] and others at the Rockefeller Institute undertook an elaborate study of oxygen therapy for those conditions in which the arterial blood was less than normally saturated as it passed through the lungs. They showed that in such conditions oxygen had great therapeutic value when administered in oxygen chambers in concentrations varying between 40 and 60 per cent. Since then the value of oxygen therapy in pneumonia, pulmonary edema and a number of other conditions has been recognized by members of the medical profession as a result of the work of many clinical investigators, especially that of Barach [6] at the Presbyterian Hospital, New York City and that of Boothby [7] at The Mayo Clinic.

The recent rapid development of commercial and military aviation has emphasized the dangers of the anoxemia to which pilots and passengers are exposed when flying. Barach [8] performed a valuable public service by emphasizing the danger to the flying public of the development of even a slight degree of anoxemia in pilots. In his paper with the startling title, " Pilot error and oxygen want," he correctly emphasized the fact that a slight degree of anoxemia, even in normal healthy men, can dull the mind and judgment sufficiently to increase the chance that a pilot would make an error which would lead to a crash. When traveling at 200 miles an hour even a slowing of the mental processes, with consequent increase in the so-called " reaction

[1] HALDANE, J. S.: The therapeutic administration of oxygen, Brit. Med. Jr., 1917, i, 181–183.

[2] STADIE, W. C.: The oxygen of the arterial and venous blood in pneumonia and its relation to cyanosis, Jr. Exper. Med., 1919, xxx, 215–240.

[3] STADIE, W. C.: The treatment of anoxemia in pneumonia in an oxygen chamber, Jr. Exper. Med., 1922, xxxv, 337–360.

[4] STADIE, W. C.: Construction of an oxygen chamber for the treatment of pneumonia, Jr. Exper. Med., 1922, xxxv, 323–336.

[5] BINGER, C. A. L.: The construction and management of an oxygen chamber, Mod. Hosp., 1925, xxiv, 186–194.

[6] BARACH, A. L.: Recent advances in inhalation therapy in the treatment of cardiac and respiratory disease, Principles and methods, New York State Jr. Med., 1937, xxxvii, 1095–1110.

[7] BOOTHBY, W. M.: Oxygen therapy, Jr. Am. Med. Assoc., 1932, xcix, 2026–2033; 2106–2112.

[8] BARACH, A. L.: " Pilot error " and oxygen want; with a description of a new oxygen face tent, Jr. Am. Med. Assoc., 1937, cviii, 1868–1872.

time," is extremely dangerous, especially if the weather is bad, visibility poor and "instrument flying" necessary. In addition, passengers who are suffering from certain cardio-respiratory difficulties, possibly without knowledge that they have such difficulties, can experience serious, sometimes even dangerous, symptoms from flying at altitudes of 5000 feet or even less, unless they are protected by efficient administration of oxygen. However, until Boothy,[9] Lovelace [10] and Bulbulian [11] recently reported the development by them of an oxygen inhalation apparatus of a mask type with rebreathing bag, especially designed to meet the needs of aviation, which needs include comfort, economical use of oxygen and noninterference with vision or with the use of the radio, it was practically impossible to supply oxygen routinely to both pilots and passengers. That the investigators have been successful in meeting these needs is evidenced by the satisfactory results of the severe tests to which their apparatus was subjected: first, in the laboratory; second, in the low pressure chamber at the Army Experimental Station at Wright Field, with the coöperation of Captain Armstrong and Doctor Heim; third, by actual flight tests through the coöperation of several of the commercial air-lines and noted aviators.

In addition, Boothby and Lovelace [12] have reported that the oxygen inhalation apparatus designed by them, in coöperation with Bulbulian, is applicable to the therapeutic administration of oxygen or of oxygen-helium mixtures. They pointed out that by its use not only can the ordinary inhalation of 50 to 60 per cent oxygen, such as is now generally accomplished in oxygen tents, be effected at about a fifth of the usual cost to the patient but that, in addition, higher concentrations of oxygen can be equally conveniently administered even up to the inhalation, when desired, of 100 per cent oxygen.

In a study, presented at a recent meeting of the Staff of The Mayo Clinic and Mayo Foundation, Boothby and Lovelace reported beneficial effects in the treatment of many conditions for which lower concentrations of oxygen had not proved efficient. They confirmed the report of Fine [13] and his associates, of Boston, that inhalation of 100 per cent oxygen would, in twelve to twenty-four hours, cause decompression of an abdomen that had become distended with gas as a result of ileus or intestinal obstruction, rendering subsequent operative treatment, if the obstruction was mechanical, a much easier surgical procedure; in some instances operation was avoided.

[9] Boothby, W. M.: Oxygen administration; the value of high concentrations of oxygen for therapy, Proc. Staff Meet., Mayo Clin. (In press.)

[10] Lovelace, W. R., II: Oxygen for therapy and aviation: an apparatus for the administration of oxygen or oxygen and helium by inhalation, Proc. Staff Meet., Mayo Clin. (In press.)

[11] Bulbulian, A. H.: Construction and design of the masks, Proc. Staff Meet., Mayo Clin. (In press.)

[12] Boothby, W. M., and Lovelace, W. R., II: Oxygen in aviation. The necessity for the use of oxygen and a practical apparatus for its administration to both pilots and passengers, Jr. Aviation Med. (In press.)

[13] Fine, Jacob, Hermanson, Louis and Frehling, Stanley: Further clinical experiences with ninety-five per cent oxygen for the absorption of air from the body tissues, Ann. Surg., 1938, cvii, 1–13.

They also confirmed the observation of Fine and his associates that in about 90 per cent of cases in which encephalography was necessary the intense headache which often follows this diagnostic procedure was either entirely avoided or the intensity of the headache was so reduced that the pain was negligible.

Some of the other conditions found by Boothby and Lovelace to be benefited by the use of high concentrations of oxygen were surgical shock, gas gangrene and tetanus. They cited a case of gas gangrene in which the subcutaneous emphysema caused by the nitrogen liberated by the bacteria had extended over the trunk and up into the tissues of the neck. In this case inhalation of 100 per cent oxygen produced rapid clinical improvement; in twelve hours the emphysema was noticeably decreased; in about thirty hours the emphysema was entirely gone and the patient was progressing rapidly to recovery.

On account of the economy and simplicity of the method of administration of oxygen devised by the Rochester investigators, it will now be possible for the internist and general practitioner to use oxygen earlier than heretofore; also, it will be possible to give oxygen efficiently in the patient's home, and hospitalization, with its attendant cost, often will be unnecessary. Likewise, the use of oxygen-helium mixtures for the relief of severe asthma is rendered practicable. In view of the recent serious European complications that almost resulted in war, it will not be out of place to suggest that this method of administration of oxygen would be of great help to surgeons of the army and navy in the treatment, on a large and economical scale, of traumatic shock, of gas gangrene and tetanus resulting from infection of shrapnel wounds, of pneumonia due to epidemic influenza or to inhalation of war gases, and many other conditions.

Karsner,[14] Barach [15] and others demonstrated, several years ago, that concentrations of oxygen in excess of 75 to 80 per cent caused pulmonary irritation and pneumonia in small animals if administered continuously for two to three days. However, neither Fine and his associates, nor Boothby and Lovelace encountered any evidence of pulmonary irritation from inhalation of 100 per cent oxygen administered for periods varying from one to three days, followed by the use of lower concentrations in a fairly extensive series of cases. Nevertheless, patients, who receive oxygen in concentrations in excess of 80 per cent, should be carefully observed and the concentration reduced at the first sign of pulmonary irritation; for the present the continuous use of high concentrations of oxygen should not exceed 24 to 48 hours.

The advantages to be gained by the use of high concentrations of oxygen are in a new field of oxygen therapy and are due to the fact that with the inhalation of 100 per cent oxygen the amount of oxygen absorbed by the

[14] KARSNER, H. T.: The pathological effects of atmospheres rich in oxygen, Jr. Exper. Med., 1916, xxiii, 149–170.

[15] BARACH, A. L.: The effects of atmospheres rich in oxygen on normal rabbits and on rabbits with pulmonary tuberculosis, Am. Rev. Tuberc., 1926, xiii, 293–316.

hemoglobin will be increased about 5 volumes per cent and the amount in simple solution will be increased about 7 volumes per cent, making a total increase in the amount of oxygen in the arterial blood of 10 to 15 volumes per cent. Furthermore, whenever the general or local circulation is slowed so that the percentage saturation of the venous blood falls to 20 or 30 volumes per cent the increase in the oxygen tension in the tissue spaces surrounding the cells as demonstrated by Campbell and Poulton [16] may be increased by as much as 50 to 75 per cent. Such an increase in the oxygen tension in the tissues often will start an upward spiral of secondary beneficial effects which will eventuate in the patient's recovery.

[16] Campbell, Argyll and Poulton, E. P.: Oxygen and carbon dioxide therapy, London, Oxford University Press, 1934, 179 pp.

REVIEWS

A Textbook of the Practice of Medicine. By various authors; Edited by FREDERICK W. PRICE, M.D., C.M., F.R.C.P., F.R.S. (Edin.). xli + 2038 pages; 14.5 × 23 cm. Oxford University Press, New York, N. Y. Fifth Edition, 1937. Price, $12.50.

This work is a textbook of medicine, suitable for the student or physician. It follows the usual plan of most modern texts, but includes a 102-page section on diseases of the skin, a subject usually omitted from American books of this type.

The volume is almost encyclopedic in its scope; some of the sections are large enough to make up individual textbooks if published separately. Thus the division on neurology contains 390 pages, and that on the Circulation 232 pages.

The publisher has produced a remarkably compact book, as the quality of paper used compensates for the presence of almost double the usual number of pages.

There is no doubt that some chapters could be improved. Thus, hypertension, storage of lead in bones, and treatment by promoting storage, are not mentioned in the discussion of lead poisoning. Potassium restriction is not recommended in the treatment of Addison's disease, though the use of cortical adrenal extract, hypodermically or orally adsorbed in charcoal, and large doses of sodium salts, are advised. Artificial pneumothorax and phrenicectomy are recommended in the treatment of bronchiectasis. Bacteremia is not mentioned in discussing the prognosis of lobar pneumonia, nor are types IV to XXXII pneumococci separated from group IV. Serum treatment of pneumonia is said to be contraindicated in advanced age.

The English custom of recommending proprietary drugs is followed. American readers of English texts would be helped by description of such remedies according to their chemical structure, or the inclusion of U.S.P. or Council accepted equivalents. Following such a practice might increase the usefulness of English books in this country.

In spite of these objections, this work is recommended as being readable, useful, well printed, and fully indexed.

T. N. C.

Introduction to Ophthalmology. By PETER C. KRONFELD, M.D., Professor of Ophthalmology, The Peiping Union Medical College. 331 pages; 15 × 24 cm. Charles C. Thomas, Springfield, Ill. 1938. Price, $3.50.

This volume on "The Introduction to Ophthalmology" has the following chapter titles: "Anatomical Introduction," "The Diseases of the Anterior Adnexa of the Eyeball," "The Diseases of the Cornea," "Uveitis," "Endophthalmitis," "The Crystalline Lens," "Injuries," "The Physiology of the Retinal Circulation," "The Vascular Diseases of the Eye," "The Intraocular Pressure and its Pathological Variations," "Neoplasms," "The Optic Nerve," "The Visual Pathway," "The Pupil," "The Motor Anomalies of the Eye," and "Refraction." There is also a combined Index and Ophthalmological Dictionary.

The material in this book does not deal to any extent with details of diagnosis, methods of examination or of treatment but, as the author states in his preface, chiefly with pathogenesis of ocular disease. Points in the anatomy and embryology of the eye are reviewed where this is found necessary to a clear understanding of the facts being presented. While the author offers his book chiefly as a supplement to short practical courses in ophthalmology, it will be found valuable to all interested in diseases of the eye.

H. F. G.

The Troubled Mind. By C. S. BLUEMEL, M.D. 520 pages; 14 × 21.5 cm. Williams and Wilkins Co., Baltimore. 1938. Price, $3.50.

The book is composed largely of psychopathology from its purely descriptive point of view. The author has collected some very interesting case material which he has presented from the standpoint of objective observations. This feature is excellent; the cases are presented concisely and interestingly. The author is particularly to be commended for his remarkable facility of exposition.

Aside from the aspect of descriptive psychiatry the book remains entirely superficial. As etiological factors in the production of mental disorder the author leans extremely to the position of "stress reactions," detailing specifically such items as broken engagements, divorce, bereavement, illness, pregnancy, childbirth, etc. The author shares the opinion of many institutional psychiatrists that mental breakdown occurs under the influence of added stress on some individual who is suffering from the vague malady known as "constitution." Early childhood stresses are minimized by the author. He even goes so far as to say (p. 67):

". . . childhood influences . . . do not always have the significance which patients attribute to them. . . . The facility of the procedure may permit the patient to overlook his inborn tendencies to specific types of response."

The author devotes a chapter to a discussion of infantalism and another to psychopathic or what he terms "infantoid" behavior. The terms are applied to the emotional rather than to the physical development. The only feature of unwholesome family influence that the author speaks about is that of overprotection. He refers to defective training from lack of discipline and to the inability of parents to allow children to do things for themselves. He fails to mention, however, the more vicious forms of parental attitudes embodied in neglect and rejection. No mention is made by the author of the need for emotional security and parental affection.

The author uses the trump card of "constitutional psychopathy" to explain many forms of aberrated behavior. His attitude towards these problems is that they consist of biological inadequacies in certain human beings. He believes that these are developmental defects in such individuals which are entirely unremediable. The only solution that society has to offer is to remove such persons from its midst. He goes on to quote such cases giving specific instances of behavior problems in children seven and eight years of age. It is the reviewer's impression that the author considers such cases as hopelessly "psychopathic," and beyond the realm of therapeutic assistance. That such a position is absurd goes without saying.

The book is obviously written to interest lay as well as professional readers. It appears somewhat too elementary for medical students (though perhaps not for some general practitioners), yet should prove interesting reading for them. The title may interest readers who already have some emotional conflicts. This can only lead to greater confusion because of the vivid descriptions of so many cases which might prove distinctly fear provoking. The author offers very little for the disturbed reader. Such advice as that "the patient should endeavor to tranquilize his life" seems to the reviewer to be quite futile in the face of a disturbing neurosis.

H. W. N.

Nursing as a Profession. By ESTHER LUCILE BROWN, Dept. Statistics, Russell Sage Foundation. 120 pages; 13.5 × 20 cm. Russell Sage Foundation, New York. 1936.

The *Evolution of the Profession of Nursing* might have been the title of *Nursing as a Profession*, one of a series of the Russell Sage Foundation monographs "dealing with the status of certain established or emerging professions in the United States."

In this monograph, Esther Lucile Brown has assembled data from various sources to show the factors responsible for the present status of nursing. The assembled facts are, on the whole, encouraging in their indication of the rise in degree of effectiveness in nursing service. Although the maximum degree of effectiveness has not been reached, the tendency is toward the rise rather than otherwise.

The interpretation given the facts presents a clear case that some branches of nursing are a profession by the six criteria set down in 1915 by Dr. Abraham Flexner who was under the impression that nursing could not meet these criteria. Approaching the answer to the question, "Is Nursing a Profession?," through evolution, the author concludes that "Nursing is moving in the same general direction as have medicine, law, dentistry, and teaching" and that "like these older professions, the personnel of each type of nursing service exhibits varying degrees of ability to accept responsibility. Such a situation, however, does not preclude recognition of professional status for the group as a whole."

One of the factors responsible for the present degree of effectiveness reached by nursing, the monograph considers "Preparation for Nursing" and the problems incident to it. The evolution of the training shows how its field of service has widened as well as its quality of service improved. From the beginning of hospital training in the nineteenth century to the twentieth century Schools of Nursing, University Schools, and Postgraduate Courses is a story of rapid evolution.

The other factor responsible for its present status of effectiveness is the four national organizations: American Nurses' Association, National League of Nursing Education, National Organization for Public Health Nursing, American Association of Collegiate Schools of Nursing.

The problems are those of supply and demand, distribution, salaries, and need for improvement in the preparation of nursing personnel for public health nursing as well as institutional nursing.

That a large part of the public fails to obtain competent nursing at the time and place necessary is because of unequal distribution in rural areas and also the infrequent "training in such specialties as psychiatry, neurology, and communicable diseases."

Besides these difficulties which nursing presents to the public, there are those to its own personnel due largely to the failures of the training "to emphasize sufficiently prevention of disease, public health nursing, or other forms of nursing given on an organized group basis to the community."

Under "Recommendation of Two Current Studies"—*Essentials of a Good School of Nursing* and *Curriculum for Schools of Nursing*—the writer presents the two studies which are based on opposite philosophies of education but reach the same conclusion or, at least, have the same tendencies in curricula for Schools of Nursing. The former centers interest on the welfare of the public—"a School of Nursing is for the patient's sake." The latter centers interest on the welfare of the nurse—a School of Nursing is for "aiding prospective nurses to adjust themselves to various social and professional situations." The difference in educational philosophy behind the two studies is more apparent than real, for both show tendencies toward the improvement of the personnel of nursing.

Under "Needed Means for controlling Standards" the monograph presents three suggested means: "A national society for accrediting schools of nursing; more adequate state legislation; a national council of state board of examiners."

Many believe that if a National Council of Nursing examiners was created, "it would lead to the evolving of more uniform requirements of nursing education, and to the harmonizing of the laws and licensure regulations of these several states."

A. C.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

Reprints

Dr. Oscar W. Bethea, F.A.C.P., New Orleans, La.—nine reprints;
Dr. Richard E. Ching, F.A.C.P., Memphis, Tenn.—one reprint;
Dr. Ralph M. Fellows, F.A.C.P., Osawatomie, Kan.—one reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—one reprint;
Dr. Louie Limbaugh, F.A.C.P., Jacksonville, Fla.—one reprint;
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Dr. Charles E. Watts, F.A.C.P., Seattle, Wash.—one reprint;
Dr. Edward E. Woldman (Associate), Cleveland, Ohio—one reprint.

Grateful acknowledgment is also made of the gift to the College Library by the Medical Protective Company of Wheaton, Ill., of a complete set of "Doctor and the Law," beginning with Volume I, No. 1, and continuing through Volume V, No. 2.

A. C. P. Board of Regents to Meet

The Board of Regents of the American College of Physicians will hold a special meeting at the College Headquarters in Philadelphia, December 18, 1938. Various committees of the College and the American Board of Internal Medicine will meet also at the College Headquarters on December 17. Important among the committee meetings will be those of the Committee on Credentials, for the examination of candidates for Associateship and Fellowship, and the meeting of the Committee on Future Policy for the Development of Internal Medicine. The latter committee is responsible for the extension of old activities of the College and for all new activities.

According to the By-Laws, proposals of candidates must be filed at least 30 days in advance of action. Members having candidates to present for action at this meeting should have their proposals filed with the Executive Secretary of the College by November 19.

Dr. Carl J. Wiggers, F.A.C.P., Professor of Physiology of the Western Reserve University School of Medicine, Cleveland, sailed from New York on September 9 for Valparaiso, going thence to Argentina. He was scheduled to deliver a series of lectures as follows: October 17, before VI Congreso National Medicina at Cordoba; October 20, Medical School, Cordoba; October 24, Medical School, Rosario; October

25, Medical School, Buenos Aires; October 26, Sociedad Argentina de Cardiologia, Buenos Aires; October 28, Academy National de Medicina, Buenos Aires.

In connection with the centennial celebration of Duke University, formerly Trinity College, Durham, N. C., the School of Medicine held a Symposium on Medical Problems, October 13, 14 and 15, 1938. Dr. Wilburt C. Davison, F.A.C.P., Dean of the School of Medicine, presided. The following Fellows contributed to the program: Dr. George W. McCoy, New Orleans, La., "Leprosy in the United States"; Dr. Charles F. Craig, New Orleans, La., "Amebiasis"; Dr. Albert Markley Snell, Rochester, Minn., "Tropical and Non-Tropical Sprue (Chronic Idiopathic Steatorrhea): Their Probable Interrelationship."

The New York Post-Graduate Medical School sponsored a Symposium on Chronic Ulcerative Colitis September 23. Dr. Philip Manson-Bahr, Director of the School of Tropical Medicine and Senior Physician at the Hospital for Tropical Diseases in London, was the guest of honor and principal speaker.

Dr. A. F. R. Andresen, F.A.C.P., Brooklyn, was the leader of the discussion on "Clinical Approach to the Problem of Ulcerative Colitis"; Dr. Z. Bercovitz, F.A.C.P., New York, presented a paper on "Diagnostic Significance of Cellular Exudate Studies in Ulcerative Colitis," which paper was discussed by Dr. Ward J. MacNeal, F.A.C.P., New York; Dr. Moses Paulson, F.A.C.P., Baltimore, gave a paper on "Diagnostic Methods in Ulcerative Colitis," and Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., gave a clinic on ulcerative colitis.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, recently received a citation "for services of distinction in the field of public health" by His Majesty, the King of Italy and Emperor of Ethiopia, who also conferred upon Dr. Geiger the Cross of Cavaliere of His Order of the Crown of Italy.

Dr. Edward Kupka (Associate), Olive View, Calif., for the ensuing year will be a Fellow at the Forlanini Institute, Rome, Italy, studying tuberculosis. He is on leave of absence from the Olive View Sanatorium.

Mr. Horace Trumbauer, Philadelphia architect, who designed the building now occupied as headquarters by the American College of Physicians, and many other important buildings in Philadelphia such as the Jefferson Medical College and Curtis Clinic, the Racquet Club, Philadelphia Free Library, etc., died September 18, 1938.

Dr. Leo V. Schneider, F.A.C.P., Glenn Dale, Md., was recently appointed Associate Clinical Professor of Medicine at Georgetown University School of Medicine, Washington, D. C.

Dr. Reid R. Heffner (Associate), formerly of the Mayo Clinic, is now located in New Rochelle, N. Y., and engaged in private practice. He was recently appointed Clinical Director of the Grasslands Hospital at Valhalla, N. Y.

The Homeopathic Medical Society of the State of Pennsylvania held its Seventy-Third Annual Session at Skytop, Pa., September 20 to 22, 1938, under the presidency of Dr. G. Harlan Wells, F.A.C.P., and the secretaryship of Dr. Donald R. Ferguson, F.A.C.P., both of Philadelphia.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., has been elected corresponding member of the Royal Italian Society of Gastro-enterology, Rome, Italy.

Dr. C. W. Waddell, F.A.C.P., Fairmont, W. Va., President of his State Medical Society, was recently appointed to the State Advisory Board of the West Virginia Department of Public Assistance.

Dr. Hugh B. Campbell, F.A.C.P., Norwich, is President and Dr. Joseph I. Linde, F.A.C.P., New Haven, is President-Elect of the Connecticut State Medical Society.

Dr. Arthur C. Christie, F.A.C.P., formerly president of the Medical Society of the District of Columbia, is the second recipient of the Frank E. Gibson Award in recognition of "meritorious contributions to medical science." The prize is presented by the Washington Medical and Surgical Society. Dr. Christie formerly was professor of operative surgery and roentgenology at the Army Medical School, professor of radiology, George Washington University Medical School and professor of clinical radiology at Georgetown University Medical School. In 1937 he was president of the fifth International Congress of Radiology, held in Chicago. He has also been president of the American Roentgen Ray Society and the American College of Radiology.

Col. Charles F. Craig, F.A.C.P., Medical Corps, U. S. Army, retired, has been made professor emeritus of tropical medicine at Tulane University School of Medicine, as of September 1. He is Editor of the *American Journal of Tropical Medicine* and Associate Editor of the *American Journal of Parasitology*.

Dr. Solomon Katzenelbogen, F.A.C.P., who has been associate professor of psychiatry at Johns Hopkins University School of Medicine, Baltimore, for several years, has accepted the appointment as director of laboratories and research at St. Elizabeths Hospital, Washington, D. C. Dr. Katzenelbogen graduated in medicine from the University of Geneva in 1918. He served as head of the laboratory of internal medicine, Medical Faculty, University of Geneva, and chief resident physician to the Hospital Canton, Geneva; he had been a member of the faculty of Johns Hopkins University since 1928 and has been in charge of the department of internal medicine at the Phipps Psychiatric Clinic in Baltimore.

Dr. James D. Bruce, F.A.C.P., Vice President in Charge of University Relations and Director of the Department of Postgraduate Medicine, University of

Michigan, Ann Arbor, delivered the postgraduate convocational address before the seventy-third annual meeting of the Michigan State Medical Society, Detroit, September 19 to 22, on "The Challenge of Medical Service."

Dr. Bruce delivered the banquet address before the Upper Peninsula Medical Society at Sault Ste. Marie, held during August, his subject being, "A Doctor's Inventory."

Dr. Charles A. Doan, F.A.C.P., Columbus, has been elected secretary of the Ohio Public Health Association.

Dr. Hans Lisser, F.A.C.P., San Francisco, and Dr. Edwin G. Bannick, F.A.C.P., Seattle, were among the guest speakers who addressed the forty-sixth annual meeting of the British Columbia Medical Association at Victoria, B.C., September 15 to 17, their subjects being "Masculinizing Syndromes; Clinical Observations on the Present Status of Gonadotropic and Sex Hormone Therapy; Indications for and Proper Use of Thyroid Substance" and "Acute Pancreatitis; Medical Treatment of Severe Burns," respectively.

Dr. Edgar Mayer, F.A.C.P., of Cornell University Medical College, New York, is a member of the committee appointed to supervise an intensive campaign against tuberculosis, as provided for in an appropriation of one million dollars by the Cuban government. Clinics have been established in Havana and Oriente, staffed by tuberculosis experts, and these clinics will eventually be extended through all sections of Cuba. Tuberculin tests will be given to adults as well as children, the survey being aimed especially at testing school children, tobacco workers and food handlers. Provision will be made for the hospitalization and treatment of those found to have tuberculosis.

Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn., and Dr. James G. Carr, F.A.C.P., Chicago, Ill., addressed the second annual symposium on occupational disease under the auspices of the department of industrial medicine of Northwestern University Medical School at Chicago, September 26 to 27.

Dr. Louis A. Van Kleeck (Associate), Manhasset, N. Y., is vice president of the New York State Association of School Physicians.

Dr. Harry A. Brandes, F.A.C.P., Bismarck, is president-elect of the North Dakota State Medical Association.

Dr. George R. Wilkinson (Associate), Greenville, S. C., has been reappointed to the State Board of Medical Examiners for four years.

Capt. Harry G. Armstrong (Associate), Medical Corps, U. S. Army, addressed the tenth annual meeting of the Aero Medical Association of the United States at Dayton, Ohio, September 2 to 4, on "Effect of Acceleration on the Living Organisms."

Dr. Paul J. Connor, F.A.C.P., Denver, has been appointed chairman of a committee to work out the details of a central service bureau to meet the demand for prepayment care, as approved by the Medical Society of the City and County of Denver. This Society also approved the plans of the recently incorporated Colorado Hospital Service Association.

Dr. George C. Stucky, F.A.C.P., formerly superintendent and medical director of the Ingham Tuberculosis Sanatorium, Lansing, Mich., has been appointed director of the Eaton County (Mich.) Health Department.

Dr. George A. Harrop, F.A.C.P., formerly associate professor of medicine at Johns Hopkins University School of Medicine, has accepted an appointment as director of research of the Squibb Institute for Medical Research, "creating in the medical and biological fields an industry-supported research enterprise." A new laboratory building has been completed at a cost of $750,000. Dr. Harrop will be in direct charge of the Institute and in addition will head the division of experimental medicine. There will be three main divisions: pharmacology, bacteriology and virus diseases and organic chemistry. There will also be a biochemical laboratory and a medicinal chemistry laboratory. The Institute was officially opened October 11, with a special program. Dr. George R. Minot, F.A.C.P., Boston, and Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn., as guest speakers, spoke on "Clinical Investigation" and "Industrial Laboratories and Clinical Research," respectively.

Among promotions recently announced on the Faculty of Western Reserve University School of Medicine, Cleveland, are the following:

Dr. Harold Feil, F.A.C.P., Associate Clinical Professor of Medicine;
Dr. Edward H. Cushing, F.A.C.P., Assistant Clinical Professor of Medicine;
Dr. Harley A. Williams, F.A.C.P., Assistant Clinical Professor of Medicine.

Dr. John B. McAlister, F.A.C.P., Harrisburg, Pa., was recently honored by a dinner by the Ex-Residents Association of the Harrisburg Hospital, celebrating the fiftieth anniversary of his internship. Dr. David Riesman, F.A.C.P., Philadelphia, was one of the speakers. Dr. McAlister graduated from the University of Pennsylvania School of Medicine in 1887. He is an honorary life member of staff of the Harrisburg Hospital and a Trustee of Gettysburg College.

Dr. Bruce H. Douglas (Associate), Detroit, has been in the Hawaiian Islands during the past summer, making a survey of the tuberculosis situation there.

Dr. Eugene R. Whitmore, F.A.C.P., Washington, D. C., is secretary of the American Association for the Study of Neoplastic Diseases.

Under the presidencies of Dr. Paul H. Ringer, F.A.C.P., Asheville, N. C., and Dr. Jesse D. Riley, F.A.C.P., State Sanatorium, Ark., the annual meeting of the Southern Tuberculosis Conference and the Southern Sanatorium Association was held in Louisville, Ky., September 19 to 21.

Dr. Henry Chesley Bush, F.A.C.P., Livermore, Calif., is president of the National Tuberculosis Association.

Dr. Thomas R. Brown, F.A.C.P., associate professor of medicine at Johns Hopkins University School of Medicine, Baltimore, and Dr. Beverley R. Tucker, F.A.C.P., emeritus professor of neuropsychiatry, Medical College of Virginia, Richmond, are members of a medical advisory board of a new 100 bed hospital for crippled children, started October 1, near Wilmington, under the auspices of the Nemours Foundation for Crippled Children. Children up to the age of sixteen years will be admitted to the hospital, but may be kept for educational purposes beyond that age, if necessary. The Foundation was provided in the will of the late Alfred I. du Pont.

Dr. Charles A. Elliott, F.A.C.P., Chicago, addressed the eighty-ninth annual session of the Indiana State Medical Association at Indianapolis, October 4–6, on "Management of Pneumonia."

Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., president-elect of the American Medical Association, was a speaker at the annual banquet of the Association, presided over by Dr. Herman M. Baker, F.A.C.P., Evansville.

Dr. Joseph McFarland, F.A.C.P., Philadelphia, delivered the Caldwell Lecture September 20 before the thirty-ninth annual meeting of the American Roentgen-Ray Society at Atlantic City, his subject being, "Keeping in Step with Science."

Dr. Clarence R. Bennett, F.A.C.P., Eufaula, Ala., is vice president of the Chattahoochee Valley Medical Association.

The Joseph N. McCormack Memorial Meeting of the Kentucky State Medical Association was held in Louisville October 3 to 6, Dr. William E. Gardner, F.A.C.P., Louisville, presiding as president.

Dr. Charles E. Sears, F.A.C.P., Portland, has been elected president of the Oregon State Medical Society.

The American Association for the Advancement of Science will hold a symposium on mental health in Richmond, Va., December 28 to 30, under the chairmanship of Dr. Walter L. Treadway, F.A.C.P., Assistant Surgeon General of the U. S. Public Health Service. There will be six sectional sessions and a general discussion session.

Dr. John H. Musser, F.A.C.P., New Orleans, and Dr. Hugh Leslie Moore, F.A.C.P., Dallas, addressed the fortieth annual convention of the American Hospital

Association at Dallas, September 26 to 30, on "Significant Nutritional Developments to be Considered in Institutional Food Service" and "Control of Infection in a Children's Hospital," respectively.

Dr. Theodore G. Klumpp (Associate) has been appointed chief of the drug division of the Food and Drug Administration, U. S. Department of Agriculture.

The Inter-State Postgraduate Medical Assembly will be held in Philadelphia, October 31 to November 4. Twenty-four members of the American College of Physicians appear as contributors to the program.

The Medical Society of the State of Pennsylvania held its eighty-eighth annual session at Scranton, Pa., October 3 to 6, 1938. Sixty-eight assignments on the program were filled by Fellows and Associates of the American College of Physicians.

Dr. Alex. F. Robertson, Jr., F.A.C.P., Staunton, Va., has been elected secretary of the Augusta County (Va.) Medical Association.

At the opening session of the Medical College of Virginia, September 19, announcement was made of the following Faculty promotions:

Dr. R. Finley Gayle, F.A.C.P., professor of neuropsychiatry.

Dr. Wyndham B. Blanton, F.A.C.P., has been made associate professor of medicine.

Dr. Beverley R. Tucker, F.A.C.P., was made emeritus professor of neuropsychiatry.

Dr. P. S. Smith, F.A.C.P., Abingdon, Va., is president of the Southwestern Virginia Medical Society.

Dr. Rudolph H. Kampmeier, F.A.C.P., has been promoted to associate professor of medicine at Vanderbilt University School of Medicine, Nashville, Tenn.

Dr. O. F. Gober, F.A.C.P., Temple, Texas, and Dr. Edward H. Schwab, F.A.C.P., Galveston, Texas, are president and secretary-treasurer, respectively, of the University of Texas Alumni.

Dr. R. J. Condry, F.A.C.P., Elkins, Dr. L. C. McGee, F.A.C.P., Elkins, and Dr. P. A. Tuckwiller (Associate), Charleston, are president, vice president and secretary, respectively, of the West Virginia Heart Association.

OBITUARIES

DR. FLETCHER JOHNSTON WRIGHT

Dr. Fletcher Johnston Wright was born in Fluvanna County, Virginia, in 1873, and died, after a brief illness, at his home in Petersburg, Virginia, May 8, 1938. He was graduated from the University College of Medicine, now the Medical College of Virginia, in Richmond, Virginia, in 1898, and spent the greater part of his professional life in the city of Petersburg, Virginia.

Dr. Wright was a man of high character, generous impulses and attractive personality and was greatly beloved by his fellow physicians. As a practitioner of medicine he was highly regarded by his colleagues and looked upon as one of the most competent men in his section. He was always active in the medical affairs of his community and of the State and held many important offices, the duties of which he discharged with fidelity and effectiveness. At the time of his death he was a member of the State Board of Medical Examiners, of the Executive Board of the Virginia Tuberculosis Association and Chairman of the Advisory Board to the Woman's Auxiliary of the Medical Society of Virginia. Dr. Wright had also served as President of the Alumni of the University College of Medicine, President of the Petersburg Medical Faculty and Vice-President of the Medical Society of Virginia. He was a member of the American Medical Association, Southern Medical Association, Tri-State Medical Association, Southside Medical Association and Fourth District Medical Society. He was a member of the staff of the Petersburg Hospital and had been an Associate of the American College of Physicians since his election in 1925.

J. Morrison Hutcheson, M.D., F.A.C.P.,
Governor for Virginia.

DR. CHARLES WILLIAM STEVENSON

Dr. Charles William Stevenson, age 49, of Wichita Falls, Texas, died July 31, 1938, in a Wichita Falls Hospital, of streptococcic bronchopneumonia.

Dr. Stevenson was born January 8, 1889, in Sutherland Springs, Texas, the son of Orrin E. Stevenson and Isabel King Stevenson. His academic education was received in the University of Texas, Austin, from which he was graduated with a B.A. degree in 1908. He then attended the Medical Department of the University of Texas for three years at Galveston, following which he taught school one year at Victoria. Resuming his medical education, he was graduated from the University of Texas School of Medicine, in 1912. After his graduation he served an internship in the Santa Rosa Infirmary, San Antonio. Following his internship, he served as assistant physician at the Terrell State Hospital, Moody's Sanitarium at San

Antonio, Dr. Greenwood's Sanitarium, Houston, and the Connecticut State Hospital at Middletown, Conn. He had lived and practiced at Wichita Falls the past eighteen years.

Dr. Stevenson had been a member of the State Medical Association and the American Medical Association through the county medical societies of his various places of residence, in 1915, 1917, 1920 to 1938. After his location in Wichita Falls, he founded The Medical and Surgical Clinic and was the head of the internal medicine and diagnostic department of that organization until his death. He had been a Fellow of the American College of Physicians since 1930. During the World War, he served as a lieutenant in the Medical Corps of the U. S. Army. Dr. Stevenson was a member of the staffs of the Bethania and Wichita Falls General Hospitals, being a past president of the staff of the latter institution. For the past twelve years, he was medical director of Dr. White's Sanitarium at Wichita Falls. Dr. Stevenson was an accomplished internist and an earnest student of medicine. He had taken post-graduate work at Washington University, the University of Pennsylvania, the University of Michigan and at many other clinical centers. He was a member of the Texas Club of Internal Medicine. He served the State Association as secretary of the Section on Medicine and Diseases of Children in 1925, and as chairman of the same section in 1937. He was vice-president of the State Medical Association in the year 1930–1931, and served the Wichita County Medical Society as president in 1932. Apart from his professional life, Dr. Stevenson was active in civic affairs. He served as a director of the Wichita Chamber of Commerce in 1934 and was a member of the Wichita Club. Dr. Stevenson was an outstanding physician and his untimely death cut short a life of usefulness in his profession.

M. D. Levy, M.D., F.A.C.P.,
Governor for Texas.

DR. PHILIP I. MARVEL, SR.

Dr. Philip I. Marvel, Sr. (Fellow), formerly one of the pioneer practitioners of Atlantic City, N. J., but living at the time of his death with his daughter at Bethlehem, Pa., died of a heart attack while hiking in the mountains near Bushkill, Pa., September 6, at the age of 81. Dr. Marvel had gone out in the mountains for a walk and when he failed to return, a searching party found him with his overcoat over his left arm and his walking cane in his right hand indicating that he had died suddenly.

Dr. Marvel, the son of Emery and Miranda Hubbard Marvel, was born on a farm in Kent County, Delaware, September 15, 1856. In eleven more days he would have been 82 years of age.

He attended the public schools of Delaware and the Wilmington Conference Academy at Dover, besides receiving private tutelage to fill in the weak spots of the graded schools of that time. Following his private

tutelage and much night study, he passed a state teachers examination and taught in the Wilmington Conference Academy for nearly four years. While teaching he decided to study medicine and matriculated in the medical department of the University of Pennsylvania in 1881 from which he graduated as M.D. in 1884. Following his graduation in medicine, he became associated with Dr. William Boardman Reed, one of the medical founders of Atlantic City, where he remained for four years.

In 1888 he practiced medicine in Washington, D. C., but returned to Atlantic City again in 1890, where he remained in active practice until his fiftieth year in medicine and retired in 1934.

Dr. Marvel was a great believer in post-graduate education and did much to advance himself along medical lines. He took postgraduate courses in New York, Berlin, London and Vienna, and came under the direct influence of men like Pasteur, Koch, Charcot and Lister.

At the time of the Johnstown, Pa., flood, Dr. Marvel was one of the first to render medical assistance and it was due partly to this terrifying experience that the Atlantic City Hospital was founded in which he served as a member of its staff for many years.

He served as President of the New Jersey Medical Society and the Atlantic County Medical Society and was a Trustee of the American Medical Association for 18 years, as well as Vice president of the A. M. A. Dr. Marvel became a Fellow of the American College of Physicians in 1921.

Dr. Marvel married Miss Rachel Irvin, daughter of Thompson and Martha Alexander Irvin of Atlantic City, November 25, 1890. Three children were born to them—Dr. Philip I. Marvel, Jr., Mrs. Joseph Boushall and Mrs. C. Cooper. Dr. Marvel was one of the oldest physicians of New Jersey at the time of his death.

He witnessed the great expansion of modern medicine from its inception at the hands of Pasteur, Koch and Lister to its full development as the profession knows it today.

Beginning as he did at the bottom of the profession, and ending after 50 years of practice upon a plane much to be envied by those with far greater opportunities, his example will be difficult to surpass and his niche in life hard to fill.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,
Governor for New Jersey.